PART 1 (OF TWO PARTS)

VOLUME 65 *January 1952* NUMBER 1

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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May 26–29, 1952

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Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N. Y.

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THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY

Medical Section of National Tuberculosis Association

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Subscription: The subscription price of the REVIEW is $10 for the calendar year. Checks should be made payable to Collier Platt, Treasurer. The price of single copies is one dollar postpaid.

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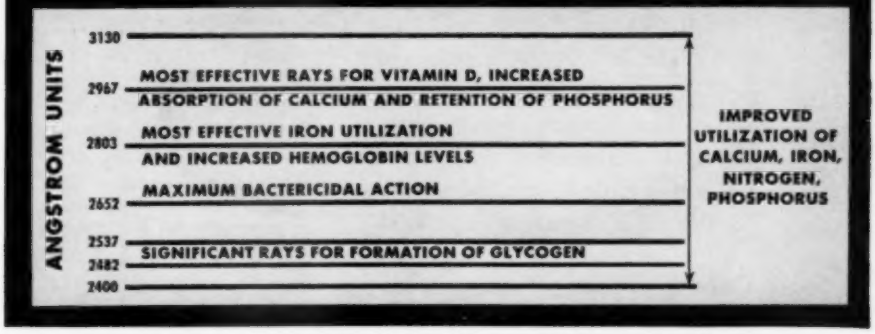

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THE AMERICAN REVIEW
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TUBERCULOSIS

VOLUME 65 *January 1952* NUMBER 1

THE TUBERCULOUS MOTHER[1,2]

A Five- to Twenty-Year Follow-up of 149 Women with 401 Full-Term Pregnancies

JACK D. COHEN, ELIZABETH A. PATTON, AND THEODORE L. BADGER

(Received for publication March 14, 1951)

INTRODUCTION

A total of 149 tuberculous mothers with 401 full-term pregnancies has been observed in the present study which represents three different groups of patients.

The first group is composed of 56 mothers in whom tuberculosis was discovered by routine roentgenographic survey of all patients who attended the Prenatal Clinic of the Boston City Hospital in 1940–1941.

The second group is composed of 25 former Boston City Hospital student nurses in whom tuberculosis was discovered by periodic roentgenographic survey while they were in training. Those who married and became pregnant were studied. Observations on this group began in 1932.

The third group is composed of 68 mothers treated at the Channing Home, a sanatorium for the care of tuberculosis. The study of this group began in 1930.

All persons have been followed for a minimum period of five years; the maximum period of study is twenty years.

The initial investigation began in 1940 with the roentgenographic survey of consecutive admissions to the Prenatal Clinic at the Boston City Hospital. The purpose was (*1*) to estimate the character of tuberculosis in a cross-section of the population of mothers who came to the Prenatal Clinic for supervision of their pregnancies; (*2*) to note the influence, if any, of gestation, parturition, and postpartum periods of pregnancy upon the course of tuberculosis; and (*3*) to determine the best form of management of tuberculosis when it occurs in the pregnant woman.

In 1948 this original Prenatal Clinic group was broadened to include the nurses and the Channing Home patients for comparative study of the interrelationships of pregnancy and tuberculosis.

[1] From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital; Department of Medicine, Harvard Medical School, Prenatal Clinic, Outpatient Department, Boston City Hospital; and the Channing Home for Tuberculosis.

[2] This study was aided by a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.

Historical Notes

Allan Krause (11), in 1935, speculated on the related effects of pregnancy and tuberculosis in a searching analysis of then current attitudes. He pointed out the widely divergent influence of pregnancy itself, of parturition, of the postpartum state, of the effects of the socioeconomic background, and of the multiparous compared with the primiparous woman. He regarded pregnancy as a normal function of the female, but a function which normal women tolerate in varied fashion, from a physiologic boon to an unmitigated evil. The physiologic effects of pregnancy upon the tuberculous woman, he thought, were not very different from those effects upon the normal woman. He searched for a relationship between the good and ill effects of pregnancy in the tuberculous and the normal woman. He recalled the age-old concept that woman's obstetrical troubles increase with her rise in the social and economic scale. He theorized upon the orderly alterations of endocrine changes that occur in the long process of childbearing.

Many of the important questions which Krause raised cannot be answered today, but this view of tuberculosis and pregnancy is one which may well be embodied in the concept of the "tuberculous mother."

No attempt has been made to exhaust past literature, as this has been done recently by R. C. Cohen (2, 3) and by A. L. Jacobs (7). However, the papers in which groups of cases with relatively long follow-up observations have been discussed will be commented upon.

Pollack and Potter (17) studied 97 pregnant women with tuberculosis. Fifty-two had active tuberculosis, 9 had collapse therapy of some sort, and 36 had healed primary or fibrocalcific lesions. There were 19 deaths among those with active tuberculosis, in 14 of whom the disease had progressed rapidly from small lesions. These authors believe that pregnancy has a deleterious effect upon tuberculosis and that only the fibrous, fibrocalcific, or healed primary disease is unaffected by it. They believe that women with active or quiescent disease should avoid pregnancy. In their opinion, the ultimate fate of the pregnant tuberculous woman is worse than that of the non-pregnant woman with similar disease. Their follow-up observation period varied from months to five years.

Seeley and associates (20) delivered 109 patients with tuberculosis. In a short follow-up, the best results were found in the group treated with collapse of the lung and in those whose treatment was begun before pregnancy, or not later than the first trimester. They believe that pregnancy has a serious effect on untreated cases.

Jameson (8) studied 451 consecutive female admissions to the Trudeau Sanatorium. He found 51 women, or 12 per cent, showing a possible relation between active tuberculosis and a preceding pregnancy. He found no significant difference in the death rate between the pregnant and the non-pregnant tuberculous patients. Parity bore no relation to the extent of the disease.

Lyman (12) studied 1,818 women with tuberculosis, 782 of whom married before sanatorium admission; 315, after discharge; and 721 remained single. Of those who married after discharge, 192 had pregnancies. This latter group continued in much better health than those who remained single and those who were married before admission to the sanatorium. In the 192 who married after sanatorium treatment, reactivation occurred within three months of delivery in 17 per cent of the cases. In those who married before admission to the sanatorium, there was a 43 per cent incidence of reactivation within three months of delivery. Lyman concluded that in the young age groups pregnancy is a risk to an active, or recently active, untreated case of tuberculosis.

Various other authors (4, 6, 9, 10, 13, 15, 16, 18, 19) present controversial evidence on the interrelationship of tuberculosis and childbearing. The view emerges, however, that

childbearing does not seriously affect the long course of tuberculosis, provided the disease is adequately treated.

PLAN OF INVESTIGATION

Prenatal Clinic Group

A roentgenographic survey of 1,450 consecutive admissions to the Prenatal Clinic of the Boston City Hospital was carried out in 1940–1941. The results are shown in the following table.

TABLE 1

INITIAL ROENTGENOGRAPHIC SURVEY OF PRENATAL CLINIC PATIENTS 1940–1941

TOTAL ROENTGENOGRAMS TAKEN—1,450	NUMBER	PER CENT
Chest films normal	1,228	84.7
Localized calcifications	143	9.9
Tuberculosis suspects	71	4.9
Cardiac disease	8	0.5
Total	1,450	100.0

This table lists 71 persons with roentgenographic densities consistent with tuberculosis. Sixty-nine of the 71 returned for completion of medical studies in 1941. Twenty-seven were shown to have active tuberculosis and received treatment. Forty-two were considered to have inactive lesions, but were not followed because of the start of World War II. Further investigation was therefore interrupted in January 1942.

In 1948–1949, a follow-up investigation was begun of the group of 69 tuberculous mothers remaining from the initial 1940–1941 survey of the Prenatal Clinic. Forty-eight of the original 69 mothers with tuberculous lesions were located for study. Fourteen were lost and 7 were dropped from the investigation as being nontuberculous. Eight new cases, collected by the same survey technique from the Prenatal Clinic during the war years 1942–1943, were added to make a total of 56 in the series. This group of 56 tuberculous mothers is restudied at this time, and their status is compared with that of other tuberculous mothers followed in similar fashion.

The Prenatal Clinic cases represent consecutive admissions, without selection. Nevertheless, they are "selected" in a sense by being limited to the low income brackets. It is a group for whom life has been a struggle for existence; a group which is always prolific and which practices little or no contraception. It is a group of persons who are often unaware of tuberculosis or have neglected its care in the hardships of living.

TABLE 2

PREVIOUSLY KNOWN AND UNKNOWN TUBERCULOUS LESIONS REVEALED BY PRENATAL CLINIC ROENTGENOGRAPHIC SURVEY

CLASS	TOTAL	TUBERCULOSIS PREVIOUSLY KNOWN	TUBERCULOSIS FIRST DISCOVERED AT SURVEY
Minimal	37	6	31
Moderately advanced	10	5	5
Far advanced	8	6	2
Unclassified	1	1	0
Total	56	18	38

Sixty-seven per cent of this group had no previous knowledge of having had tuberculosis. Eighty-one per cent of those discovered for the first time had minimal tuberculosis.

Social studies: Each patient was interviewed in the home by the social worker for evaluation of socioeconomic factors.

Housing: Evaluation of living conditions was based on technical information on houses and definitions obtained from the Boston Housing Authority (25). A poor home refers to a dwelling that is run down, with repairs neglected; one which has a toilet but no bathtub, or with such facilities shared by more than one family. Poor dwellings contained less than the Boston standard of an average of one room per person.

TABLE 3

TYPES OF HOMES OCCUPIED BY PRENATAL CLINIC GROUP

Tenements	27
Housing projects	8
Apartments	7
Own home	6
	48

The distinction between an apartment and a tenement is that an apartment has central heating, while a tenement does not. All families living in public housing facilities were judged to have good homes, as were others with well-repaired adequate homes. Twenty-seven improved their housing over the years; 21 stated conditions were the same or worse.

Income: Budgets for each family were evaluated on a minimum income basis with standards for food, rent, fuel, light, clothing, household supplies, and carfare established by the Community Health Association (26). Detailed budgets were estimated in 45 of the 56 families. Thirty-five of these 45 families lived on budgets below minimal standards.

Diet: Dietary information was based on a week's diet evaluated medically; "very poor" was grossly inadequate in all components; "average" was well balanced; "excellent" was more than adequate in all requirements. Such estimates must, of course, be approximations only.

Work history: The term "overwork" is used to describe mothers who were obliged to supplement the family income by outside employment in addition to their household duties.

Living conditions of the persons who comprise this group present a bitter commentary on the squalor and poverty of lives that have been neglected (table 4). From the viewpoint of this study, they clarify to some extent the bacillus-host relationship in the natural history of tuberculosis. In spite of inadequate diets and incomes, as well as poor homes and overwork, 38 of the 56 clinic mothers showed good progress in their recovery in the follow-up period. This observation will be discussed later as an expression of constitutional factors of resistance to tuberculosis.

Nurses' Group

The nurses' group is composed of 25 former student nurses of the Boston City Hospital in whom tuberculosis was discovered by periodic roentgenographic and tuberculin surveying every six months while in training (1). The nurses with tuberculosis reported in this study were trained at the Boston City Hospital between 1932 and 1944. They were known to have developed tuberculosis during this period, and all of them subsequently married and had children. This group has been followed, up to 1949 (1). On the whole, they are young women from good homes, with adequate family incomes and with good marital adjustments in later years. Following their marriage they showed little change in their social and economic status, evaluated by the same criteria as outlined for the Prenatal Clinic group.

The great contrast of living conditions between the Prenatal Clinic patients and the

nurses is shown in table 4. In regard to contact history, the family was the chief source in the clinic group, and occupational contact was the chief source in the nurses group.

Channing Home Group

The Channing Home group represents patients who were admitted to the sanatorium for the treatment of active pulmonary tuberculosis. This institution is a small 29-bed hospital in Boston for women with tuberculosis.

Nearly half of the patients had far advanced cavernous tuberculosis on admission. They were treated with strict bed rest, twenty-four hours a day, supplemented by whatever collapse procedures were needed. Patients admitted between 1930 and 1944 were studied with follow-up observations extending to 1949.

TABLE 4

COMPARISON OF SOCIAL, ECONOMIC, AND OTHER FACTORS IN THOSE LIVING AND DEAD OF TUBERCULOSIS

Prenatal Clinic and Nurses' Groups

	TOTAL CASES	LIVING CONDITIONS				CONTACT HISTORY			WORK HISTORY		MARITAL HISTORY
		Inadequate Diet	Poor Home	Inadequate Income	Overwork	Family Contact	Husband Contact	Other Contact	Working Before Onset	Working After Treatment	Poor Marital Relationship
Prenatal Clinic											
Stationary or improved	38	22	23	34	14	9	2	1	10	6	6
Progressed	11	6	7	8	5	6	1	1	4	3	2
Dead	7	2	3	1	0	2	0	0	0	0	2
Nurses											
Stationary or improved	16	1	0	0	0	0	0	16	16	9	0
Progressed	9	1	0	2	0	0	0	9	9	3	0
Dead	0	None	—	—	—	—	—	—	—	—	—

These three groups thus constitute the working basis for comparative study and analysis. Each is unique in its own way. Each is in reality a "selected" group, though randomized by survey selection in the case of the clinic and nurses' groups, and by routine hospital admission in the Channing Home group. The Prenatal Clinic patients are a "selected" group by virtue of their socioeconomic contrast to the others. The Channing Home cases are "selected" by virtue of their being hospitalized for active tuberculosis. The nurses are a more homogeneous group. There has been no selection of *cases* in any group. All cases were included as they were discovered by roentgenographic survey or clinical diagnosis.

OBSERVATIONS

One hundred forty-nine mothers had 442 pregnancies in the total series. There were 41 known miscarriages, leaving 401 full-term deliveries. These data are

presented in table 5. The average number of pregnancies per mother in each group studied is shown in table 6.

It is apparent that most of the children originate from the low-income group. In the Clinic group the relationship of the number of pregnancies to the tuberculosis mortality is shown in table 7.

TABLE 5

TOTAL PREGNANCIES, MISCARRIAGES, AND FULL-TERM BIRTHS

149 Women with 401 Full-Term Pregnancies

GROUP	NUMBER OF MOTHERS	TOTAL PREGNANCIES	MISCARRIAGES	FULL-TERM BIRTHS
Prenatal Clinic	56	214	15	199
Nurses	25	50	0	50
Channing Home	68	178	26	152
Total	149	442	41	401

TABLE 6

AVERAGE NUMBER OF PREGNANCIES PER MOTHER BY GROUPS

Prenatal Clinic group	4.2
Nurses' group	2.0
Channing Home group	2.5

TABLE 7

NUMBER OF PREGNANCIES AND THE COURSE OF TUBERCULOSIS IN 56 MOTHERS FROM THE PRENATAL CLINIC OVER A FIVE- TO TWENTY-YEAR PERIOD

INITIAL DISEASE CLASSIFICATION	COURSE	TOTAL NUMBER OF MOTHERS	AVERAGE NUMBER OF PREGNANCIES
Minimal	Improved or stationary	29	4.6
	Progressed	6	3.2
	Died	3	3.3
Moderately advanced	Improved or stationary	3	4.3
	Progressed	5	2.6
	Died	2	1.5
Far advanced	Improved or stationary	6	4.8
	Progressed	0	0
	Died	2	4.0
Total		56	

A total of 20.1 per cent of the mothers died of tuberculosis in the three groups. This represents a mortality rate of 2.6 per 100 mothers per observation year.

Pathologic Type of Disease in Relation to the Course of Tuberculosis

The course and end results based on the pathologic type of disease are seen in table 8. This table also shows the incidence of the various pathologic types of

disease in the three groups studied. Sixty-seven per cent of the clinic patients, all ambulatory, were unaware of their disease. They had a preponderance of fibrotic lesions. Those whose disease healed without treatment represent a selected group in the sense of being endowed with a high constitutional resistance to tuberculosis.

The group of nurses whose primary active disease occurred when they were students had had predominately exudative disease. Their early tuberculous le-

TABLE 8

THE COURSE AND END RESULTS OF TUBERCULOSIS IN THE FIVE- TO TWENTY-YEAR FOLLOW-UP OF 149 MOTHERS, BASED UPON THE PATHOLOGIC TYPE OF DISEASE AT ONSET OF STUDY

GROUP	TYPE OF TB AT ONSET OF STUDY	TOTAL CASES	COURSE		END RESULT		
			Stationary or Improved	Progressed	Arrested	Active	Dead of TB
Prenatal Clinic (56)	Fibrotic	32	29	3	29	1	2
	Exudative	18	6	12	12	2	4
	Cavernous	4	1	3	1	2	1
	Unclassified	2	2		2		
	Total	56	38	18	44	5	7
Nurses (25)	Fibrotic	3	3		3		
	Exudative	20	12	8	17	3	
	Cavernous	1	1		1		
	Pleurisy with effusion	1		1	1		
	Total	25	16	9	22	3	0
Channing Home (68)	Fibrotic	2	2		2		
	Exudative	23	16	7	16	3	4
	Cavernous	37	18	19	18		19
	Pleurisy with effusion	2	2		2		
	Unclassified	4	4		4		
	Total	68	42	26	42	3	23

Fibrocalcific lesions are included under the classification of fibrotic.

sions were discovered soon after development through routine roentgenographic survey every six months. These lesions, for the most part, were 1 to 3 cm. in diameter, similar to those described by Medlar (14) as exudative bronchopneumonia. In addition to early discovery and early treatment, these lesions were arrested before marriage and childbearing. The disease in every case was *early tuberculosis* in a limited community of nurses, living under similar conditions in hospital quarters, and with frequent contact with open cases of tuberculosis on the wards.

The Channing Home group represents patients admitted with acute disease of varied duration. Of the total patients, 34 per cent were classified as having predominantly exudative tuberculosis and 54 per cent as having cavernous tuberculosis. This group with exudative and cavitary disease combined had a mortality of 40 per cent or, more accurately, a death rate of 2.9 per 100 patients per year. In contrast, those with only fibrotic lesions showed no deaths in the follow-up.

Anatomic Extent of Tuberculosis

The initial and final classification of tuberculosis based on the anatomic extent of disease is shown in table 9. Here again the study of individual groups shows the Prenatal Clinic patients and the nurses to have minimal disease principally which, for the most part, remained minimal and fibrotic through the final observations of the study.

The Channing Home patients, on the other hand, with 53 per cent with disease classified as far advanced, showed an over-all mortality of 33.8 per cent. Those who survived did well. The results are shown by comparison of initial classification with the final classification according to the anatomic extent of the disease (table 9).

Deaths shown in total numbers are expressed both as a percentage and as a rate per 100 mothers per observation year. Inasmuch as each group was followed for a variable period of years, the percentage rate is not a true expression of the facts. Since there were no deaths among the nurses, only the Prenatal Clinic and Channing Home groups are compared. The over-all death rate of 2.9 per 100 mothers per year in the latter group is significantly greater than the rate of 1.8 per 100 per year as shown in the Prenatal Clinic group. Patients with lesions originally classified as far advanced showed a far higher mortality than patients with lesions originally classified as minimal.

Treatment

The treatment used varied widely, and the over-all picture is reflected in table 10. Slightly more than 50 per cent of the Prenatal Clinic group, with predominantly fibrotic and minimal lesions, received no special treatment. The disease in these cases was considered inactive and was watched in those who would report for check-up. Reclassification of the disease of these patients at the end of the study verified the initial diagnosis of inactive disease as shown in tables 8 and 9. In this group of mothers, there was an inherent disregard for treatment. This was a result of their conviction that they would be able to handle their tuberculosis. With many, however, the difficulties entailed in clinic visits were due to family responsibilities. The very fact that this group did so well in spite of more numerous pregnancies and poor living conditions is an indication that they represent a "survival of the fit" or, in other words, a group with extraordinarily good constitutional resistance to tuberculosis. The detailed record of their case histories is indeed a dramatic story in many instances. Those in the clinic group who received collapse procedures of any sort had more advanced disease than those in the nurses' group and the Channing Home patients. In

TABLE 9

Total Cases of Tuberculosis

Anatomical Classification of Total Lesions at Onset of Observation and at End of Study Five to Twenty Years Later

Group and Date	Initial Classification		Final Classification 1949							
			Final Anatomical Classification of Survivors				Death and Mortality Rates of TB			
	Anatomic Classification	Number of Cases	MIN.	M.A.	F.A.	No Classification	Number	Per cent	Number of Observation Person Years	Rate per 100 per Year
Prenatal Clinic 1941-1942	MIN.	37	31	2	1		3	8.0	265	1.1
	M.A.	10	1	4	3		2	20.0	73	2.6
	F.A.	8	0	2	4		2	25.0	32	6.3
	Unclassified	1				1				
	Total	56	32	8	8	1	7	12.5	370	1.8
Nurses' Group 1932-1944	MIN.	21	19	2	0		0	—		
	M.A.	4	0	4	0		0	—		
	F.A.	0	0	0	0		0	—		
	Total	25	19	6	0		0	—	—	—
Channing Home Patients 1930-1944	MIN.	12	12	0	0		0	—	132	—
	M.A.	20	11	3	1		5	25.0	421	1.2
	F.A.	36	5	3	8		18*	50.0	226	7.9
	Total	68	28	6	9	1	23*	33.8	779	2.9
Grand Total		149	79	20	17	1	30*	20.1	1,149	2.6

Min.—minimal.
M.A.—moderately advanced.
F.A.—far advanced.
* Two deaths from nontuberculous disease not included.

TABLE 10

The Effect of All Treatments upon the Course of Tuberculosis in 149 Mothers with 401 Full-Term Pregnancies

Group	Course of the Disease	Total Number of Cases	Total Number with Sanatorium Treatment	Left Sanatorium Against Advice	Pneumothorax Treated Only	Thoracoplasty	Excision Surgery
Prenatal Clinic (Total = 56)	Improved or stationary	38	12	5	11	6	
	Progressed	11	8	2	5	0	
	Dead	7	7	3	3	0	
Nurses (Total = 25)	Improved or stationary	16	8	1	4	0	
	Progressed	9	8	3	3	0	
	Dead	0	0	0	0	0	
Channing Home (Total = 68)	Improved or stationary	41	41	3	23	5	3
	Progressed	4	4	0	1	0	0
	Dead	23	23	4	5	5	1
Totals (149)		149	111	21	55	16	4

other words, they waited longer to seek help for their tuberculosis. The 6 thoracoplasty patients in the Prenatal Clinic group did well. All 6 went through subsequent pregnancies without reactivation of their disease, and none died of tuberculosis during the study period. Pneumothorax was, on the whole, less satisfactory. Eleven did well, 5 progressed to thoracoplasty, and 3 died. The failure of pneumothorax appears, however, to have been due to poor selection of cases. The 5 patients who required thoracoplasty subsequently did well.

The treatment of the nurses' group while in training was primarily bed rest for their early lesions. Of the 7 treated with pneumothorax, 4 had very satisfactory results. In 3, the lesions progressed temporarily, but the end results were satisfactory, nonetheless.

TABLE 11

FIVE- TO TWENTY-YEAR FOLLOW-UP OF 55 TUBERCULOUS MOTHERS TREATED WITH ARTIFICIAL PNEUMOTHORAX

GROUP	END RESULTS OF TECHNICALLY "SUCCESSFUL"* PNEUMOTHORAX CASES							END RESULTS OF TECHNICALLY "UNSUCCESSFUL" PNEUMOTHORAX CASES					
	Total	Arrested		Active		Died of TB		Total	Arrested Re-expanded		Active	Died of TB	
		Number	Per cent	Number	Per cent	Number	Per cent		Number	Per cent		Number	Per cent
Prenatal Clinic	10	8†	80.0	1	10.0	1	10.0	9	2	22.0	5	2	22.0
Nurses	6	5	83.0	1	17.0	0	0	1	0	0	1	0	
Channing Home	23	22‡§	96.0	0	0	1‖	4.0	6	1¶	17.0	1	4	67.0
Total	39	35	90.0	2	5.0	2	5.0	16	3	19.0	7	6	38.0

* "Successful" = cavity closure, sputum conversion, and loss of toxicity.
† One unexpanded.
‡ Two unexpanded.
§ One died of leukemia.
‖ Reactivated four years after re-expansion of successful pneumothorax.
¶ Died of suicide.

The Channing Home group, treated with absolute bed rest and with temporary or permanent collapse when indicated, showed either very satisfactory results in the twenty-year follow-up or a fatal termination. This high mortality is indicative of a low constitutional resistance to tuberculosis in those who submitted to excellent treatment but failed to do well in the long run. Pneumothorax results are presented in table 11 as end results in technically successful and unsuccessful pneumothorax. "Technical success," as used here, indicates a good mechanical collapse obtained with or without pneumonolysis. An "unsuccessful pneumothorax" indicates one in which the diseased portion of the lung could not be successfully collapsed or one in which other complications, such as fluid, necessitated its abandonment before a reasonable period of time had elapsed. The value of a successful pneumothorax is apparent in table 11. It is clear that

the patients who were treated satisfactorily with pneumothorax did well along with the extra burden of childbearing.

Thoracoplasty was carried out on 16 mothers. All of the 6 in the clinic group did well with subsequent pregnancies, and none died or progressed. All of these thoracoplasties were followed by a six-month period of strict bed-rest treatment. In the Channing Home group there were 10 thoracoplasties. Five of the patients did well and 5 died of tuberculosis.

The record of 5 of the 6 in the clinic group who did well with surgical collapse is as follows: The first patient had thoracoplasty in 1934 and had four children from 1942 to 1948 without reactivation. The second patient had an unsuccessful pneumothorax followed by thoracoplasty in 1935, and subsequently had three uncomplicated deliveries in 1938, 1942, and 1947, without reactivation of her tuberculosis. The third patient required thoracoplasty seven years after her only pregnancy. The fourth, showing reactivation after each of her three pregnancies, subsequently had a successful thoracoplasty. The fifth had surgical collapse in

TABLE 12

RELATION OF 401 FULL-TERM PREGNANCIES TO INITIAL ACTIVITY OR REACTIVATION OF TUBERCULOUS LESIONS REPRESENTING 149 MOTHERS

GROUPS	OCCURRENCE OF TUBERCULOUS ACTIVITY RELATED TO GESTATION AND SUBSEQUENT YEARS						Total
	Before Gestation		During Gestation or the First Postpartum year		More than One Year Post Partum		
	Number	Per cent	Number	Per cent	Number	Per cent	
Prenatal Clinic	138	69.0	25	13.0	36	18.0	199
Nurses	44	88.0	3	6.0	3	6.0	50
Channing Home	39	26.0	22	14.0	91	60.0	152
Total	221	55.0	50	13.0	130	32.0	401

1938 after her third delivery, followed by four more pregnancies from 1940 to 1945 without reactivation. The 5 cases above were all in the "inadequate income" group. The details of one case are incomplete.

Association of Activity of Tuberculosis with Gestation and the First Postpartum Year

The time-relationship of activity of tuberculosis to pregnancy and the postpartum period is shown in table 12. No instances of activation were related to parturition itself. There appears to be no specific time limit to the so-called postpartum period, according to the obstetrical authority, O. R. Eastman (5), except that endocrine functions are usually back to normal three months after delivery. Many mothers, however, do not regain normal menstruation for nine months to a year after childbearing. The postpartum period in this study is arbitrarily defined as the first year after delivery.

The selection of one year as the postpartum period may not be absolutely correct, but in a chronic recurrent disease, such as tuberculosis, this time period has been selected in order to align relationships of tuberculous activity to child-

bearing. Based on this definition, 50, or 13 per cent, of the 401 full-term pregnancies could be shown to bear a definite relation to activity of tuberculosis during gestation or in the first postpartum year, as shown in table 12.

Fifty-five per cent, or more than one-half, of all of the instances of active tuberculosis existed before the occurrence of any pregnancies; 13 per cent of the activations showed a clear-cut association either with pregnancy or with the first postpartum year; and 32 per cent of the activations occurred more than one year after the first postpartum year. It is further observed that it was the Prenatal Clinic group, picked up by survey for the most part, whose tuberculosis occurred early, with relatively few reactivations following the first postpartum year in spite of their very large families. Morever, the nurses, with six exceptions, who treated their tuberculosis as students did well during gestation and subsequently. The Channing, or sanatorium-treated patients, on the other hand, appear to represent a group with chronic recurrent tuberculosis, persons inherently

TABLE 13

COMPARISON OF TUBERCULOSIS ATTACK RATES DURING: (a) GESTATION (b) FIRST YEAR POST PARTUM, AND (c) MORE THAN ONE YEAR POST PARTUM, AS SHOWN IN 180 FULL-TERM PREGNANCIES*

GROUPS	DURING GESTATION			1 TO 12 MONTHS POST PARTUM			MORE THAN ONE YEAR POST PARTUM		
	Number of Cases	Total Observation Years	Attack Rate per 100 per Year	Number of Cases	Total Observation Years	Attack Rate per 100 per Year	Number of Cases	Total Observation Years	Attack Rate per 100 per Year
Prenatal Clinic (61)	20	148.0	13.5	5	199.0	2.5	36	278.6	12.9
Nurses (6)	1	37.5	2.6	2	50.0	4.0	3	50.0	6.0
Channing Home (113)	6	114.5	5.2	16	152.0	10.5	91	574.0	15.8
Total (180)	27	300.0	9.0	23	401.0	5.5	130	912.6	14.2

* Excluding the 221 instances of activation of disease occurring before gestation.

more susceptible, whose disease showed its maximum number of active periods occurring after the first postpartum year.

The Attack Rate in Association with Gestation and Subsequent Years

In table 13 is presented the attack rate of active tuberculosis, whether initial infection or reactivation of previous disease, per 100 persons per year for the gestation period, for the first postpartum year, and subsequently. This modifies the results shown in table 12 by reducing them to the common denominator of *time* based upon total observation years as well as on number of cases. The *total observation years* of cases appearing more than one year post partum were computed by the sum total of: (*1*) those years between any two pregnancies dated one year after delivery of one pregnancy to nine months before the next delivery and (*2*) all the pregnancies occurring more than one year after the last delivery to the end of the study. On this basis, therefore, there were numerous mothers

whose pregnancies occurred in such rapid succession that there were no observation years unassociated with gestation or the first postpartum year until after the last child was born. An "attack rate" before gestation could not be satisfactorily worked out.

The Prenatal Clinic group, with the largest families and poorest living conditions, showed its highest rate during gestation and its lowest rate in the first postpartum year.

This finding is not entirely satisfactorily explained by an analysis of the group, but may be due to inaccuracies in the years when cases were not under our observation.

The number of nurses with reactivation of disease as shown in table 13 is too small for estimating "significance," but the breakdown rates of the Prenatal Clinic and Channing Home groups show "statistically significant" variations although different trends in their rates. The Channing Home rate increases steadily as the time from delivery increases, as would be expected. This attack rate roughly parallels the natural history of tuberculosis mortality rates and is similar to that of the non-pregnant tuberculosis patient. The Prenatal Clinic group does not seem to follow any pattern.

The nurses, though few in number, paralleled the Channing Home patients in their attack rate through gestation and the postpartum year.

Comparison of rates: Comparison of these rates with other groups is unsatisfactory. The Boston City Hospital nurses had an attack rate of 0.97 for all cases during their observation years but this included the 90 per cent who never developed any signs of tuberculosis as well as those who had tuberculosis. Here, it is a matter of *reactivation* of tuberculosis in those who were known to have had it, for the most part, before they ever became pregnant. Thus, we are dealing with a supposedly infected group with demonstrable infection previous to, or at the time of, initial observation. Therefore, the rate should be higher in this whole group with at least roentgenographic evidence of tuberculosis, old or new. Nonetheless, these rates fail to show any striking effects of gestation for the first postpartum year except: (*1*) in the gestation period of the Prenatal Clinic group, and (*2*) in the postpartum year of the Channing Sanatorium group.

In terms of individual mothers, 75 per cent showed no activity of tuberculosis related at any time to their numerous pregnancies. Twenty-five per cent of the mothers showed tuberculous activity associated with one or more of their pregnancies.

Relation of activity to gestation in fatal cases of tuberculosis: A comparative view of the relation of tuberculous activity to gestation and the first postpartum year in all 30 mothers who eventually *died of tuberculosis* is shown in table 14. In this table it is shown that 47 per cent of the persons who died showed a relation of tuberculous activity to the process of childbearing. This table also depicts the number of mothers in whom reactivation of disease occurred during or after pregnancy. More than half, or 53 per cent, of these cases of fatal tuberculosis showed no relation to pregnancy or the postpartum period. The 47 per cent of the reactivations of the fatal cases associated with pregnancy may be compared with

the over-all picture in which only 25 per cent of the total 149 mothers showed a definite relation of disease activity to the childbearing period.

Lack of consistency between activity and different pregnancies: Table 14 is presented to show the inconsistency of activity of tuberculosis in the course of repeated pregnancies. There is no pattern of behavior to be anticipated except that those who eventually died of tuberculosis handled their tuberculosis during, or soon after, pregnancy relatively poorly. This is to be expected, and it cannot be said that pregnancy and childbearing were or were not the principal factors in activating the tuberculosis. Constitutional susceptibility is implied in those who die of tuberculosis. In those with inherently poor resistance to tuberculosis, it

TABLE 14

ONSET OF ACTIVE TUBERCULOSIS OR REACTIVATION IN RELATION TO PREGNANCY AND THE POSTPARTUM PERIOD IN THIRTY MOTHERS WHO SUBSEQUENTLY DIED OF TUBERCULOSIS

	APPEARANCE OF ACTIVE TUBERCULOSIS IN TIME RELATION TO SPECIFIC PREGNANCIES							
	During Pregnancy		1 to 6 Months After Pregnancy		7 to 12 Months After Pregnancy		1 Year or More After Pregnancy	
	Number of Cases	Number of Pregnancies	Number of Cases	Number of Pregnancies	Number of Cases	Number of Pregnancies	Number of Cases	Number of Pregnancies
	3	p^1	1	p^2	1	p^1	3	p^1
	2	p^2	1	p^3	3	p^2	5	p^2
			1	p^4			5	p^3
			1	p^8			1	p^4
			1	p^{14}			1	p^8
							1	p^{10}
Total	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
30	5	17.0	5	17.0	4	13.5	16	53.0

p = pregnancy.
Prime numbers indicate pregnancy with which activity was associated. e.g.,
p^1 = first pregnancy.
p^2 = second pregnancy.
p^{14} = fourteenth pregnancy, et cetera.

does not take much strain to throw the balance of power in favor of the infecting organism.

Tuberculous mothers who failed to experience reactivation during pregnancy: Analysis of the data shows that 111, or 75 per cent, of the 149 mothers went through numerous pregnancies with *no* associated reactivation of tuberculosis as compared to the 38, or 25 per cent, who did show activity related to pregnancy. Were there special differences in these two groups that distinguished one from the other in their reactions to childbearing? Could differences in the pathologic type of disease, in the anatomic extent of tuberculosis, in the size of the family, or differences in the nature of treatment account for differences in behavior of disease in one or the other group?

Total experience in relation to pregnancy: In table 15 is summarized the total experience with 149 mothers divided into the 38 whose disease was related, compared to the 111 whose disease was unrelated, to pregnancy. It is clear from this table that those who handled their tuberculosis well had predominantly fibrotic lesions that were minimal in extent with generally *satisfactory* results of treatment. The same amount of exudative disease was present in both groups, but those with disease activity which was related to pregnancy or to the postpartum

TABLE 15

ANALYSIS OF TUBERCULOUS ACTIVITY IN 149 MOTHERS WITH 401 FULL-TERM PREGNANCIES

Comparison of the 25 Per Cent Whose Activity Was Related to Gestation or the First Postpartum Year, with the 75 Per Cent Showing No Such Association

GROUP	RELATION OF ACTIVE DISEASE TO PREGNANCY	TOTAL MOTHERS	PATHOLOGIC TYPE OF DISEASE AT ONSET OF STUDY				EXTENT OF DISEASE AT ONSET OF STUDY				MEAN FULL-TERM PREGNANCIES PER MOTHER	RESULTS—ALL TREATMENTS		
			Fibrotic	Exudative	Cavernous	Unclassified	Min.	M.A.	F.A.	Unclassified		Satisfactory		Unsatisfactory
												Treatments	No treatment recommended	
Prenatal Clinic	27 per cent related	15	20.0	66.0	14.0	0	27.0	33.0	40.0	0	3.1	80.0	0	20.0
	73 per cent unrelated	41	71.0	20.0	7.0	2.0	80.0	10.0	8.0	2.0	3.7	29.0	66.0	5.0
Nurses	8 per cent related	2	0	50.0	50.0	0	50.0	50.0	0	0	2.0	50.0	0	50.0
	92 per cent unrelated	23	13.0	87.0	0	0	87.0	13.0	0	0	1.9	87.0	0	13.0
Channing Home	31 per cent related	21	0	33.0	66.0	0	10.0	38.0	52.0	0	2.4	52.0	0	48.0
	69 per cent unrelated	47	9.0	38.0	47.0	6.0	21.0	26.0	47.0	6.0	2.3	68.0	0	32.0

The "Pathologic Type of Disease," the "Extent of Disease," and "Results—All Treatment" are expressed in percentages.

Min.—minimal.

M.A.—moderately advanced.

F.A.—far advanced.

period had lesions which were predominantly cavernous and far advanced in extent. The size of the family and the socioeconomic status seemed to be less influential than the pathologic type and extent of intrinsic tuberculosis.

The 27 per cent of the Prenatal Clinic group whose active tuberculosis *was* related to childbearing did as well as the over-all average and better than the Channing Home group of sanatorium-treated patients. This again reflects the inherently high constitutional resistance of the clinic mothers since, in spite of

their tuberculosis, they were ambulatory and in charge of large and active families.

The nurses illustrate the fact that those who had minimal disease and received treatment early did well in the course of raising their families. Because of the routine six-month roentgenographic examination of all nurses at the Boston City Hospital, all of their lesions were discovered as *early* disease and, therefore, essentially exudative in type, as shown by Medlar (14).

The Channing Home group, in contrast to the others, represents patients with largely far advanced, cavernous tuberculosis. In spite of well-supervised treatment, end results in the sanatorium group were less satisfactory than with the other two groups. As shown in table 9, 33 per cent of this group died, with a mortality rate of 2.9 per 100 per year, a rate considerably greater than the 1.8 rate of the clinic group whose regard for treatment was comparatively casual and whose living conditions were the worst in the city.

TABLE 16

THE END RESULTS OF 19 CHANNING HOME MOTHERS WITH A HISTORY OF MISCARRIAGES

INITIAL CLASSIFICATION	NUMBER OF CASES	END RESULTS	
		LIVING	DEAD
Minimal	2	2	0
Moderately advanced	6	4	2
Far advanced	11	0	11
Total	19	6	13

Miscarriages

There were a total of 42 known miscarriages in 31 mothers. There may well have been others not reported. Furthermore, information about these 42 miscarriages was not readily offered and is therefore incomplete. Only the data on the 19 Channing Home patients with 26 miscarriages were sufficiently accurate to present in table 16 below. In this group, tuberculous activity occurred in 5 of the 19 persons during the gestation period or within the first year after miscarriage.

No interpretation of the results in this small series can be made. Other normal pregnancies occurred in each of these mothers so that end results cannot be evaluated on the basis of any single factor.

Comparison of Mortality in Tuberculous Mothers Compared to Tuberculous Females Never Pregnant

A study has been made of 68 consecutive admissions to the Channing Home of tuberculous females who had never been pregnant. The comparison of this group with the pregnancy group is remarkably similar, and anatomic classifications and mortality rates are shown in table 17. The cases present an interesting similarity in numbers and types of disease. The final results show a slightly higher mortality

rate in the non-pregnancy groups, but this difference is not considered statistically significant.[3] This comparison further substantiates the view that women with approximately the same extent and type of tuberculosis handle this disease quite similarly whether they are mothers or not. It suggests that factors other than gestation and parturition play an important part in the reactivation of tuberculosis which is associated with childbearing.

TABLE 17

MORTALITY RATE IN 68 CONSECUTIVE TUBERCULOUS MOTHERS COMPARED WITH 68 CONSECUTIVE TUBERCULOUS FEMALES WHO WERE NEVER PREGNANT. From Channing Home Cases Only

CLASSIFICATION	TOTAL CASES	INITIAL CLASSIFICATION				DEATHS		MORTALITY RATE	
		Min.	M.A.	F.A.	Unclassified	Number	Per cent	Number Observation Years	Rate per 100 per Year
Tuberculous mothers	68	12	20	36	0	23	33.8	779	2.9
Tuberculous females never pregnant	68	6	20	37	5*	28	41.2	709	3.9

* Unclassified because of: thoracoplasty on admission, 3; pneumothorax on admission, 2.
Min.—minimal.
M.A.—moderately advanced.
F.A.—far advanced.

DISCUSSION

The evidence obtained from the present study can incriminate neither the childbearing incident nor other specific factors related to pregnancy as potentially dangerous for tuberculosis. The anatomic extent of disease, the pathologic pattern, and the native resistance or susceptibility of the individual patient to tuberculosis appear from the study to be the essential factors which determine the course and prognosis of the tuberculous mother.

Pregnancy is an extra burden, physically and physiologically, for any woman, no matter how easily she may carry and deliver her child. It was not possible to demonstrate a statistically significant difference in end results between the pregnant and the non-pregnant group.

It is clear from the present study that the best management of the tuberculous mother is the treatment of her own particular type of tuberculosis with all the resources at our disposal. The natural course of pregnancy seems little affected but it should be supervised with the usual precautions of a normal pregnancy. In addition, the mother should have whatever treatment is indicated for the best care of the tuberculosis per se, regardless of the pregnancy.

Most important of all, every pregnant woman should have a chest roentgenogram at the beginning of her first pregnancy, whether or not she is known to have, or is suspected of having, tuberculosis. With the discovery of a lesion or the

[3] Analysis by Dr. Jane Worcester, Professor of Biostatistics, Harvard School of Public Health.

knowledge of an old one, management of the case will then be guided by the nature of the underlying tuberculosis, whether it is active or inactive, whether it is new and undiscovered disease or an old and known infection with an established pattern of behavior.

Mothers with inactive, old fibrotic and fibrocalcific tuberculosis do well and have been shown in this study to have an excellent prognosis through numerous pregnancies. Moreover, mothers have done well with minimal exudative tuberculosis which has been treated early in its course and arrested a year or more before the onset of pregnancy. This is seen especially in the nurses' group. Since 13 per cent of the 401 full-term pregnancies were shown to have some relation of activity to pregnancy or the first postpartum year, however, all of those with lesions should have periodic clinical and roentgenographic evaluation every three months during pregnancy, immediately post partum, and every three months during the first postpartum year. For the subsequent two years the lesion should be followed every six months; thereafter, every year, indefinitely. This is approximately the regimen recommended for any person with a newly discovered lesion, the status of which is not definitely determined.

Active tuberculosis discovered at any time in pregnancy, or any other time, requires strict bed rest with whatever collapse procedures or chemotherapy are indicated for the type of disease. Tuberculous pleurisy with effusion demands the same treatment as other forms of tuberculosis: bed rest for four to eight months, with modified and progressive activity for another four to eight months. Chemotherapy dosage is referred to later in the present study.

Collapse of the lung: The indications and contraindications for pneumothorax, surgical collapse of the lung, and excision surgery are the same as for non-pregnant tuberculous patients. Suffice it to say that a specific treatment should, or should not, be used according to the indications predicated by the character of the tuberculosis. Modification of treatment because of associated pregnancy is rarely necessary.

Technically successful pneumothorax (as defined above) has been shown in the present study to be an effective and useful form of therapy for cavitary disease. Table 11 is of interest in this regard. In spite of the unpopularity of pneumothorax today, it remains good treatment in the wisely selected case and should not be discarded until better results can be shown by other methods.

Surgical collapse and excision of the lung may be carried out at any time during pregnancy if control of the disease by such procedures is indicated. On general principles, however, the third trimester of pregnancy should not be disturbed by any major surgery unless absolutely necessary because of the possibility of inducing premature delivery. Moreover, most mothers do so well with good medical care that emergency chest surgery is rarely necessary at that time.

Streptomycin: Streptomycin was not used in any of the study cases since it was not available at that time. At the present time, however, it is being used by the writers during pregnancy for the same indications and in the same dosages as with the non-pregnant female. In 2 of the cases in which 1 gm. of streptomycin was administered to the mother daily for 45 days, there were no ill effects upon

the child. A third mother is under treatment with streptomycin, 1 gm. twice weekly, and para-aminosalicylic acid (PAS), 12 gm. daily. Dawson (28) reports the similar use of streptomycin in three tuberculous mothers, one with 1 gm. of streptomycin daily for 42 days; another, 1 gm. daily for 21 days; the third, with intermittent therapy. All three had normal babies without detectable ill effects from streptomycin. Blake (23) reports the use of streptomycin in four mothers during pregnancy without deleterious effects upon the fetus.

Rogers, Wilson, and Goodier (30) report a mother who developed acute miliary tuberculosis eight weeks before term. Three grams of streptomycin daily for a total of 300 gm. prolonged the mother's life to delivery of a normal child who showed no evidence of tuberculosis or ill effects from the streptomycin. The pregnancy in this case did not appear to be influenced by the disease or treatment with streptomycin. The child's tuberculin test has remained negative.

Rubin, Winston, and Rutledge (33) report three gravid women with active tuberculosis who received 1 gm. of streptomycin daily for 23 to 30 days during mid and late pregnancy. Neurologic examination with vestibular tests of the three infants up to one and one-half years of age revealed no evidence of drug damage.

The data at hand, however, are not adequate, particularly in terms of sufficient follow-up observations, for final analysis of any streptomycin effect upon the fetus. It has been shown by Lincoln and Kirmse (31) that small children tolerate streptomycin in larger doses than adults, with few evidences of significant neurotoxicity. The writers have been unable to find any reports of the ill effects of streptomycin upon the fetus and believe such an occurrence would be unlikely, at least with modern doses of the drug.

Streptomycin now is being used by the writers for the tuberculous mother in doses comparable to those used in the non-pregnant patient; 1 gm. twice a week, together with para-aminosalicylic acid, to tolerance up to a maximum of 12 gm. daily. The gastrointestinal symptoms of the latter drug may be exaggerated during early pregnancy and it may need to be omitted temporarily. The sodium salt has been better tolerated. These dosages are based upon the published experience of the Veterans Administration (27) obtained in pulmonary tuberculosis but unassociated with pregnancy.

Pneumoperitoneum: Pneumoperitoneum was unpopular previous to 1944 and, hence, was not used as a collapse procedure during the course of this study. Subsequent experience with it, however, has proved its usefulness when initiated after delivery in exudative and cavitary lesions in the lower two-thirds of the lung. It has been the practice of the writers, in a few selected cases, to initiate pneumoperitoneum three or four days after delivery. An authoritative opinion (29) has recently been obtained, however, that there is no reason why pneumoperitoneum should not be initiated immediately after delivery. The basal cavitary lesion in acute tuberculosis is unsuited by location for pneumothorax or surgical collapse. This lesion should receive streptomycin, but it has also proved suitable for pneumoperitoneum, preferably with temporary phrenic compression on the affected side. Such a lesion at the base of the lungs is reasonably regarded as

being precariously placed immediately after delivery when the previously high diaphragm suddenly drops down. It is for this purpose that pneumoperitoneum is recommended soon after delivery. However, detailed discussion of this problem is deferred until data on ventilatory studies in normal pregnancy by Cugell, Gaensler, and Badger (24) at the Boston City Hospital have been completed.

Termination of pregnancy: The termination of pregnancy has not often been recommended to the mothers in this study because of local hospital rules forbidding its use and because predominant religious beliefs are opposed to it. The reader is referred to the recent works of Studdiford (22) on this subject. Floyd (32), in his treatment of pulmonary tuberculosis in pregnant women, gives considerable space to the matter of "abortion." However, in the light of modern therapy for tuberculosis, the proper treatment of the disease seems more important than the termination of the pregnancy except in the individually selected case. It has been the practice of the writers to recommend any interruption only within the first four months of pregnancy, if at all. No formula has been evolved for the use of termination as a form of therapy, for it has so rarely been necessary. Far advanced exudative or cavitary disease and the early initial infection of unknown prognosis in the young mother deserve the most serious consideration concerning interruption.

In general, however, it is believed that the tuberculosis should receive the best of treatment while the normal course of pregnancy is continued. The bad results of pregnancy associated with tuberculosis are very often due to poor or inadequate medical treatment. Such a situation should not be allowed to cloud the issue of interrelated effects. Good and thorough treatment for the tuberculosis must be established whenever reactivation occurs during or after gestation, else it cannot be said that pregnancy has favorably or unfavorably influenced the course of the disease in any person. In other words, treat the tuberculosis and watch the growing child.

The present study has shown that mothers who receive good treatment for their tuberculosis before pregnancy have done well with the whole cycle of childbearing, be it one incident or many. Out of this experience with mothers who have experienced activation of their tuberculosis in association with gestation or the first postpartum year, certain recommendations have emerged:

1. Those mothers treated for minimal tuberculosis are advised to let two years elapse with their disease in an arrested state before becoming pregnant. 2. Those with moderately advanced disease should have three years with disease in an arrested state before reproducing. 3. Those with far advanced tuberculosis have such a poor prognosis with or without pregnancy that they are advised to defer childbearing until it is clear that treatment by whatever means employed has established an arrested and stable lesion for at least five years.

Mothers with active tuberculosis should neither nurse nor care for their babies until all contagiousness is gone and recovery warrants the extra burden of work. Furthermore, they should continue sanatorium care or its equivalent as long as the nature of the tuberculosis requires it.

The management of the tuberculous mother will continue to impose some restriction in daily living, no matter what size the family: more rest at night, a midday rest, and avoidance of prolonged fatigue. Time and careful yearly clinical and roentgenographic follow-up will reveal the inherently resistant and the susceptible individual. There are those in whom the natural factors of immunity will permit many pregnancies and hard work without effect upon existing tuberculosis. There are others in whom the margin between susceptibility and immunity is a narrow one and in whom the strain of any added responsibility, be it a pregnancy, family or social duties, or lack of sleep, is enough to reactivate an otherwise quiescent or arrested lesion. From the present study, however, it is difficult to specifically credit gestation or the first postpartum year with any special deleterious influence upon the course of tuberculosis.

SUMMARY

One hundred and forty-nine mothers with 401 full-term pregnancies have been followed five to twenty years. The study is composed of three groups: (a) 56 mothers from the Prenatal Clinic of the Boston City Hospital; (b) 25 mothers, formerly student nurses at the Boston City Hospital, with tuberculosis discovered by periodic survey; and (c) 68 mothers admitted to the Channing Home for Tuberculosis. Each is a selected group for a variety of reasons.

Mothers with minimal fibrotic or fibrocalcific tuberculosis and minimal exudative disease treated and arrested one or more years before pregnancies had the best prognosis.

Patients with far advanced cavernous tuberculosis had the worst prognosis.

In 13 per cent of 401 full-term pregnancies, the patients showed activity of disease associated with gestation or the first postpartum year.

The number of children in the family did not appear to be an important factor in activation of the mother's tuberculosis.

Activation of tuberculosis, if it occurred in relation to one or, rarely, two pregnancies, was likely to be followed or preceded by other normal pregnancies.

The natural history of tuberculosis was greatly varied in the three groups studied.

SUMARIO

La Madre Tuberculosa. Observación durante Cinco a Veinte Años de 149 Mujeres con 401 Embarazos a Término

Ciento cuarenta y nueve madres con 401 embarazos a término fueron mantenidas en observación durante cinco a veinte años. El estudio comprende tres grupos: (a) 56 madres de la clínica prenatal del Hospital de la Ciudad de Boston; (b) 25 madres, ex-estudiantes de enfermería del mismo hospital, en las que las encuestas periódicas revelaron tuberculosis; (c) 68 madres recibidas en el sanatorio para tuberculosos del Asilo Channing. Cada uno de ellos constituye un grupo seleccionado por varias razones.

El mejor pronóstico correspondió a las madres con tuberculosis fibrosa o fibrocalcificada mínima y exudativa mínima tratadas y estacionadas desde uno o más años antes del embarazo.

El peor pronóstico recayó sobre las enfermas con tuberculosis cavernosa muy avanzada.

Trece por ciento de 401 embarazos a término mostraron actividad de la enfermedad asociada con la gestación o con el primer año postpuerperal.

El número de niños en la familia no pareció constituir un factor importante en la desintegración.

El desencadenamiento de la tuberculosis, si ocurrió en relación con un embarazo, o raramente, con dos embarazos, fué susceptible de ir seguido o precedido de otros embarazos normales.

La historia natural de la tuberculosis varió considerablemente en los tres grupos estudiados.

RESUME

La Mère tuberculeuse: Observations poursuivies pendant des périodes de cinq à vingt ans chez 149 femmes ayant eu 401 grossesses à terme

Cent quarante-neuf mères ayant eu 401 grossesses à terme, ont été observées pendant cinq à vingt ans. L'étude a porté sur trois groupes: a) 56 mères de la clinique pré-natale du "Boston City Hospital"; b) 25 mères, anciennes élèves infirmières du "Boston City Hospital" et dont la tuberculose avait été décelée au cours d'enquêtes périodiques; c) 68 mères admises au "Channing Home", sanatorium pour tuberculeux. Chacun de ces groupes a été selectionné pour diverses raisons.

Chez les mères atteintes de tuberculose fibreuse ou fibrocalcique minime avec exudat peu accentué, et dont l'affection avait été traitée et arrêtée un an ou plus avant la grossesse, le pronostic était le meilleur.

Chez les malades présentant des lésions cavitaires avancées, le pronostic était le plus mauvais.

Dans 13% des cas, sur 401 grossesses à terme, l'évolution de la tuberculose se poursuivait au cours de la grossesse ou pendant la première année post-partum.

Le nombre d'enfants dans la famille ne paraît pas été un facteur exerçant une influence importante dans la réactivation de la tuberculose.

La réactivation de la tuberculose qui s'est produite à l'occasion d'une ou, rarement de deux grossesses, a été le plus souvent suivie ou précédée par d'autres grossesses normales.

L'évolution naturelle de la tuberculose varie beaucoup dans les trois groupe étudiés.

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TUBERCULOSIS IN ANTHRACOSILICOSIS[1,2,3]

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(Received for publication May 18, 1951)

INTRODUCTION

The inhalation of dusts containing free silica causes pulmonary fibrosis and emphysema with resulting impairment of respiratory function, and it appears that silica favors the development of tuberculosis. The controversial issues relate to the clinical incidence of the combined diseases and the criteria for diagnosis. In the present report the studies of anthracite coal miners are considered with special reference to the frequency of tuberculosis as established by clinical investigation.

The concept that silica renders the lung susceptible to tubercle bacilli was initiated by reports from South Africa, where 75 per cent of gold miners showed on post-mortem examination evidence of associated tuberculosis (1). Subsequent studies abroad and in the United States, particularly those of Lanza and Vane (2) Riddle (3), and Gardner (4, 5), have largely supported this concept. Kettle (6) has shown that tubercle bacilli injected intravenously multiplied rapidly in necrotic tissues produced by the previous local injection of silica particles, whereas no unusual growth occurred when other irritants were used. Gardner (5) demonstrated that tubercle bacilli of low virulence, ordinarily nonpathogenic for guinea pigs and rabbits, induced progressive disease in the silica-exposed animals. It was assumed by these investigators that silica sensitized the tissues previously refractory to the microorganisms. Recent experimental evidence has further shown that the BCG strain of tubercle bacilli produces a progressive and fatal form of pulmonary tuberculosis in guinea pigs whose tissue resistance has been modified by the inhalation of quartz dust (7).

The divergent reports on the incidence of tuberculosis in silicosis are illustrated as follows: Boehme (8) noted tuberculosis in 19.3 per cent of 126 autopsied stone cutters; and Gooding (9) found the disease in 24.5 per cent of the autopsies on 230 South African hard coal miners. Sander (10), in a survey of workers in foundry and granite industries, recorded an incidence of active tuberculosis of only 3 per cent. Charr and co-workers (11) reported evidence of tuberculosis at post-mortem examination in 28.1 per cent of a group of anthracite miners and a rate of 10.4 per cent in a similar group of non-miners. More recently, Stewart (12), in a follow-up study of some 400 hard coal miners, found evidence

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[2] This study was aided by a grant from the Anthracite Health and Welfare Fund of the Jefferson Medical College Hospital.

[3] Presented before the Medical Session, as part of the symposium on *Nontuberculous Diseases of the Chest and Related Matters* at the 47th annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, on May 18, 1951.

of active tuberculosis in less than 3 per cent after exposure to silica dust had ceased.

The reported high prevalence of tuberculosis in silicosis and the concept of increased susceptibility have been questioned. Ornstein and Ulmar (13), Auerbach (14), and Auerbach and Stemmermann (15) believe that the coexistence of silicosis and tuberculosis in the same lung is entirely coincidental and that the growth of the tubercle bacillus is not stimulated by the silicotic fibrosis. They emphasize that the older concepts are based chiefly on vital statistics, and they consider the figures misleading. It is mentioned especially that the diffuse fibrosis of silicosis with impaired pulmonary function and superimposed infection produces a form of pulmonary disease indistinguishable from tuberculosis and that the diagnosis of tuberculosis is all too frequently made incorrectly, even when tubercle bacilli are not found in the sputum.

The present study relates to the statistical analysis of tuberculosis associated with silicosis, or so-called anthracosilicosis, which occurred in an unselected group of anthracite coal miners (750 cases) from Pennsylvania. Included in the findings are data on the length of exposure to coal dust, the onset of manifest tuberculosis, and the course and criteria for diagnosis. It should be mentioned, in considering the contributing factors of silicosis with complicating tuberculosis, that carbon dust alone does not produce lesions similar to those of silicosis. While anthracite contains 6 to 13 per cent of free silica, it is known that the dusts in coal mines may contain total silica up to 63 per cent (16). The higher percentages are found in gangways, rock tunnels, and chutes, where jack hammers and blasting operations are employed.

METHOD OF STUDY

The group of 750 hard coal miners with various stages of anthracosilicosis was hospitalized for periods of two to three weeks from 1946 through 1950. With the exception of 113 men (15 per cent), all were sufficiently disabled to have discontinued working before admission. The clinical studies included medical and occupational history, physical, fluoroscopic, and roentgenographic examinations, bronchoscopy, sputum and pulmonary function tests, and chemical determinations of certain substances in the blood. Persons with unproved but suspected tuberculosis were generally readmitted after three to six months for further investigation or were transferred to the White Haven division for continued observation.

Occupational history: The duration and circumstances of underground exposures to dust were recorded in order to throw light on the rate of development of silicosis. There was special inquiry as to the type of work, such as operations in slopes, gangways, chutes, and long tunnels; and data likewise were obtained on steady or intermittent employment.

Medical history: The past incidence of repeated chest colds, pleurisy, pneumonia, and heart disease was noted, with special reference to the effects or relation to cough, expectoration, dyspnea, hemoptysis, weakness, weight loss, fever, and night sweats. The acute episodes of acute respiratory symptoms were differentiated, so far as possible, from the persistent manifestations of the chronic pulmonary condition. The actual causes for cessation of work were recorded.

Physical examination: The following observations were noted: general nutrition, pallor, cyanosis, clubbing of the fingers, curvature of the nails, dyspnea at rest, movements and measurements of the thorax, and alterations in the percussion note and breath sounds. The occurrence and character of rales were tabulated as dry (musical) or moist, localized or generalized, and transient or persistent. The heart was examined for evidence of enlargement, murmurs, and irregularity of action.

Laboratory studies: The amount of sputum expectorated in 24 hours was measured in grams and its character noted. All specimens were tested routinely by microscopic examination for tubercle bacilli and, if negative, three or four 24-hour specimens were similarly examined consecutively. If sputum negative for tubercle bacilli persisted, a 24-hour concentrate, a 72-hour concentrate, and three examinations of the fasting gastric contents were made. One of the 24-hour specimens was also cultured for tubercle bacilli. Additional sputum examinations and cultures were made at the White Haven Sanatorium in cases with sputum persistently negative for tubercle bacilli.

Other laboratory studies included a urinalysis, complete blood count, erythrocyte sedimentation rate (Westergren method), fasting blood sugar, serologic test for syphilis, urea nitrogen, and determination of the serum proteins, albumin, and globulin. Tuberculin testing with first- and second-strength purified protein derivative (PPD) was done in all cases.

Fluroscopy and roentgenography: Each patient was fluoroscoped, and variations of the diaphragmatic excursions, abnormalities in the size and contour of the heart, and the presence of cavities with shifting fluid levels were noted. Roentgenograms were obtained during deep inspiration and full expiration in the conventional posterior-anterior and lateral planes. Planigraphy and bronchography were employed in cases of suspected cavities and bronchiectasis; roentgenograms of other parts of the body were taken as required.

Bronchoscopy: Bronchoscopy was employed in cases of suspected bronchial obstruction and of infection with sputum negative for tubercle bacilli. Bronchial secretions were examined routinely for tubercle bacilli by smear and culture and, when indicated, for neoplastic cells.

RESULTS OF STUDY AND ANALYSIS OF DATA

The diagnosis of active reinfection-type pulmonary tuberculosis was established in 97 cases, or 12.9 per cent of the total number studied. This was based on the demonstration of acid-fast bacilli in the sputum in all cases but one; and, in the exception, tubercle bacilli were found in the sputum before admission to the hospital. In 7 additional cases (0.9 per cent) a diagnosis of healed tuberculosis was made, based on the previous history of active tuberculosis and the characteristic roentgenographic findings; and in 8 other cases (1.1 per cent) tuberculosis was suspected on the basis of abnormal roentgenographic and clinical findings although tubercle bacilli had not been found in repeated sputum examinations. In one of these suspected cases with a draining sternal sinus, tuberculosis was proved by examination of material obtained at biopsy. Including the cases diagnosed without the support of laboratory findings, the incidence of tuberculosis was 14.9 per cent.

Data obtained from the history of the proved cases of tuberculosis are recorded in figures 1 and 2 and in tables 1, 2, 3, and 4.

Occupational Findings

Exposure to silica varied from 13 to 50 years, the average period being 29.1 years. Exposure was underground except in one instance, the majority of miners

(77 per cent) having employed a jack-hammer or hand machine. In one case, with employment above ground in a breaker shed, the concentration of dust was as great, if not greater, than underground. It was noted in figure 1 that tuberculosis became manifest most frequently in those with 20 to 40 years of underground exposure to silica dust.

Medical Findings

It is noted that tuberculosis occurred in all age groups; the youngest miner was 33 years of age, the oldest 67 years. The highest incidence of tuberculosis occurred in the fourth and fifth decades of life (75 per cent), as shown in figure 2.

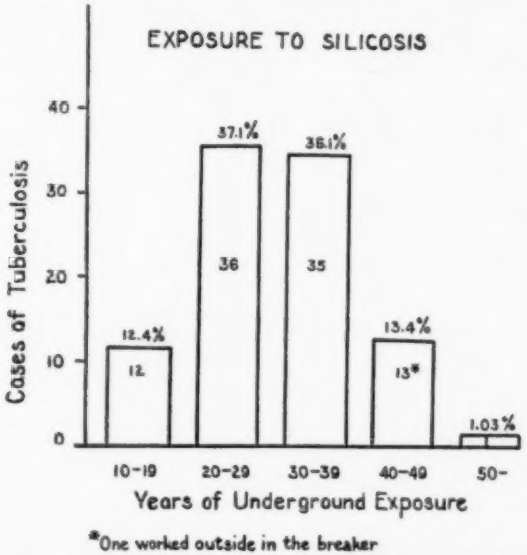

FIG. 1. Relation of tuberculosis to length of underground exposure to silicosis. Tuberculosis occurred most frequently in those with twenty to forty years' exposure.

When analyzed in relation to the total group of disabled miners (figure 3), it can be seen that the prevalence shows a sharp drop in the older age groups. The infection was present in only 2 miners less than 35 years of age. Between the ages of 35 and 44, tuberculosis was diagnosed in 23.8 per cent of cases; at ages 45 to 54, in 15.6 per cent; at ages 55 to 64, in 9.0 per cent; and at ages above 65, in 6.9 per cent. As compared to the findings in a group of male industrial workers (17), it would appear that tuberculosis was approximately eight times as prevalent among this group of miners in the age group 35 to 44; approximately three times as prevalent in the age group 45 to 54; and approximately equal in prevalence for the ages above 55 years.

A history of previous respiratory infection (disabling colds, bronchitis, pleurisy,

or pneumonia) was noted in 64 per cent of the total number studied and in 60 per cent of the proved cases of tuberculosis (table 1). Tuberculosis itself, either proved or suspected, was recorded in 31 men (4.1 per cent of the total group, 22.7 per cent of the tuberculous group). In only 20 of these men, however, was the diagnosis verified by subsequent sputum examinations. This emphasizes that the history may be erroneous.

Cessation of work: The medical histories indicate that certain tuberculous miners continued work without knowledge of their tuberculosis; others stopped

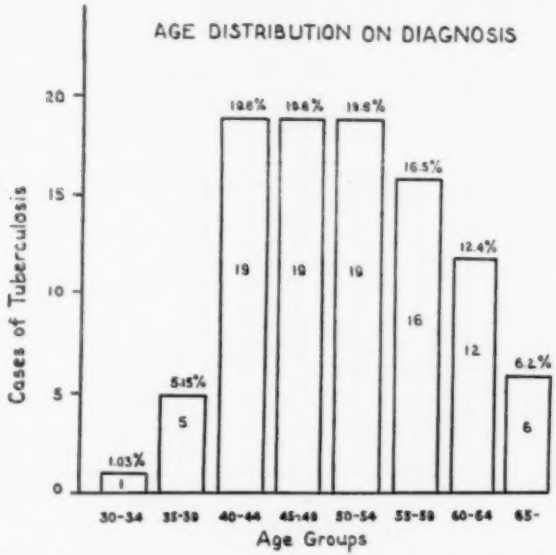

FIG. 2. Age distribution of hard coal miners at time of diagnosis of tuberculosis. The complication appeared most frequently in the age groups from forty to sixty years.

because of the manifestations of tuberculosis or silicosis. This is illustrated in the following figures: 8 miners were still working at time of admission, and the remaining 89 had varying complaints (table 2) which had prompted discontinuance of work a few days to 18 years prior to admission, the average period of work stoppage being 2 years. In only 9 cases (9.3 per cent) was work terminated because of the diagnosis of tuberculosis, although a prior diagnosis had also been made in 12 other cases. In 58 per cent of the group, the miner was forced to stop work and leave the mines because of various degrees of dyspnea usually attributed to silicosis. The pattern of dyspnea was similar to that seen in uncomplicated silicosis. In the tuberculous cases, however, sudden acute exacerbation of the dyspnea coincident with activation of the infection was

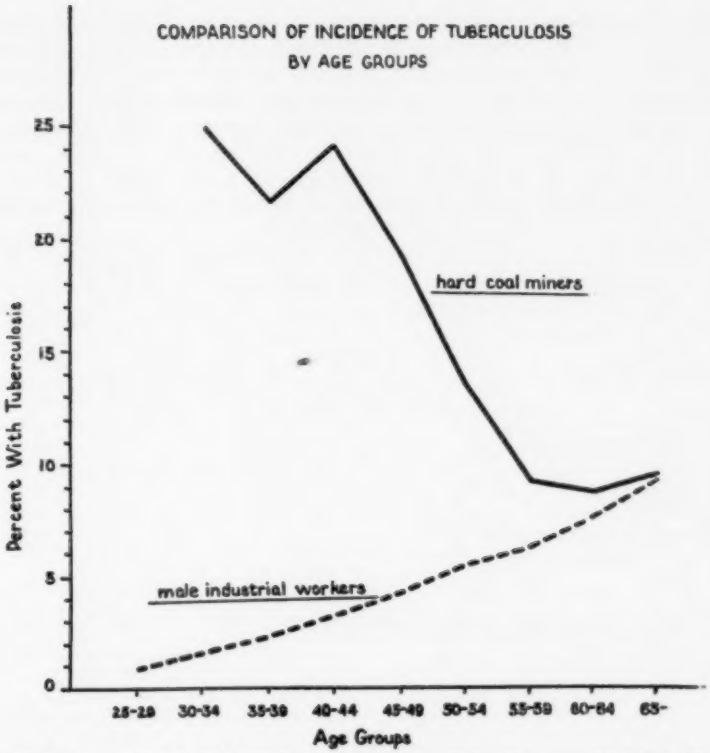

FIG. 3. Comparison of incidence of tuberculosis by various age groups in 740 hard coal miners (solid line) and 39,002 male industrial workers (broken line).

TABLE 1

SILICOTIC MINERS INCLUDED IN STUDY AND THOSE WITH PROVED TUBERCULOSIS, CLASSIFIED BY HISTORY OF PAST ILLNESS

HISTORY OF PAST ILLNESS	SILICOTIC MINERS IN STUDY		MINERS WITH PROVED TUBERCULOSIS	
	Number	Per cent distribution	Number	Per cent distribution
Total	750	100.0	97	100.0
Disabling colds	235	31.3	26	26.8
Pneumonia	133	17.7	19	19.6
Pleurisy	78	10.4	12	12.4
Bronchitis	34	4.5	1	1.0
Tuberculosis	31	4.1	22	22.7
History not reported	239	32.0	17	17.5

frequently experienced and precipitated work stoppage. Acute "chest colds" were considered the cause for cessation of work in 11 cases, although it was probable that some of these were actually exacerbations of the underlying tuberculous infection. Hemoptysis, though present in 35 per cent of the group, was given as the cause for leaving the mines in only 3.1 per cent of the cases.

TABLE 2

SILICOTIC MINERS WITH PROVED TUBERCULOSIS, CLASSIFIED BY CHIEF CAUSE FOR WORK STOPPAGE

CHIEF CAUSE FOR WORK STOPPAGE	SILICOTIC MINERS WITH PROVED TUBERCULOSIS	
	Number	Per cent distribution
All causes	97	100.0
Dyspnea	56	57.7
"Chest cold"	11	11.3
Diagnosis of tuberculosis	9	9.3
Weakness	4	4.1
Hemoptysis	3	3.1
Non-medical reasons	6	6.2
Still working up to admission	8	8.2

TABLE 3

SILICOTIC MINERS WITH PROVED TUBERCULOSIS, CLASSIFIED BY PRESENT SYMPTOMS

PRESENT SYMPTOMS	SILICOTIC MINERS WITH PROVED TUBERCULOSIS	
	Number	Per cent distribution
Total	97	100.0
Weight loss	85	87.6
Cough	83	85.6
Expectoration	81	83.5
Dyspnea	79	81.4
Weakness	74	76.3
Chest pain	50	51.5
Elevated temperature	37	38.1
Hemoptysis	34	35.1
Night sweats	15	15.5

Non-medical causes for work stoppage were injuries, advanced years, or closure of the mines, and accounted for a frequency of 6.2 per cent.

Symptoms on admission: The symptoms on admission are recorded in table 3. Loss of weight, noted in all but 12.4 per cent of cases, was slight (1 to 10 pounds) in 10 cases, moderate (11 to 20 pounds) in 33 cases, and severe (more than 21 pounds) in 42 cases. Cough and expectoration were present in approximately 80

per cent of the cases, and dyspnea occurred in 81.4 per cent. Dyspnea appeared early in the course of the disease and was more gradual in onset in men in whom tuberculosis was present in the simple nodular type of silicosis. In patients with tuberculosis and massive conglomerate silicosis, dyspnea was frequently more sudden in onset and of shorter duration before disability resulted. Dyspnea was closely associated with weakness, loss of weight, elevated temperature, and "acute chest colds." Chest pain occurred in one-half of the cases, but true pleuritic pain was rare. Hemoptysis, varying from slight streaking to massive hemorrhage, occurred in 35 per cent, a slightly higher frequency than was noted in the nontuberculous cases. In 37 patients there was an elevation of temperature from 99.2° to 101° Fahrenheit. Night sweats were infrequent except in miners with advanced tuberculosis. It was striking that the symptoms, in varying combination, in 31 patients showed sudden and pronounced aggravation prior to cessation of work, suggesting an acute extension of the tuberculous processes.

TABLE 4

SILICOTIC MINERS WITH PROVED TUBERCULOSIS, CLASSIFIED BY FINDINGS ON PHYSICAL EXAMINATION

FINDINGS ON PHYSICAL EXAMINATION	SILICOTIC MINERS WITH PROVED TUBERCULOSIS	
	Number	Per cent distribution
Total	97	100.0
Localized moist rales	44	45.4
Nutritional status:		
Poor	38	39.2
Fair	34	35.1
Good	25	25.8
Abnormal breath sounds	27	27.8
Impairment on percussion	23	23.7
Curvature of finger nails	19	19.6
Clubbed fingers	14	14.4
Musical rales	7	7.2

Physical Examination

The significant findings are shown in table 4. Emaciation was common. Clubbing of the fingers was present in 14 patients, while curvature of the finger nails occurred in 19, a significant frequency as compared with the lower incidence in nontuberculous coal miners. Reliance for the diagnosis of tuberculosis was mainly on the presence of abnormal breath sounds and localized moist rales, generally in the upper lobes, found in 45 per cent of the group. These findings suggested the diagnosis before tubercle bacilli were found in the sputum. Percussion of the chest was considered unreliable, since the emphysema obscured the tuberculous lesion except when consolidations were close to the periphery of the

lung. Alterations of the breath sounds were present in 28 per cent of the group. Localized rales of the fine and coarse varieties, precipitated by coughing, occurred in 44 cases. Musical or dry rales, as noted in 7 cases, were related to associated emphysema in the nontuberculous area of the lungs. The pulse was generally above 100 per minute, a finding not present in those classed as having nonspecific secondary infection.

Laboratory Findings

Sputum: The amount of sputum varied from 5 to 115 gm. in 24 hours (average, 37 gm. per patient). Acid-fast bacilli were detected eventually in the pulmonary secretions in all but one case. The Gaffky count varied from 1 (6 cases) to 10 (2 cases), the majority showing Gaffky 4 or 5.

TABLE 5

SILICOTIC MINERS WITH PROVED TUBERCULOSIS, CLASSIFIED BY METHOD OF DETECTING ACID-FAST BACILLI

METHOD OF RECOVERY	SILICOTIC MINERS WITH PROVED TUBERCULOSIS	
	Number	Per cent distribution
Total	97	100.0
Direct smear of sputum	83	85.6
Upon readmission or subsequent admission to other hospitals	6	6.2
Bronchial secretions (direct smear)	5	5.2
Sputum concentrate	1	1.0
Sputum culture	1	1.0
Sputum positive for tubercle bacilli prior to hospital admission	1	1.0
Fasting gastric contents	—	—

As seen in table 5, tubercle bacilli were detected in a simple direct smear of the sputum in 83 cases. Of this group, the first specimen was positive in 73 instances, and in the remaining cases acid-fast bacilli were found in the second or third specimens. It is interesting that the bacilli were recovered in only one concentrate after the plain smears had been negative; and in no case were bacilli recovered from smears of the fasting gastric contents. One culture positive for *M. tuberculosis* was obtained when the simple smears, concentrates, and gastric contents were negative. In 5 additional cases, acid-fast bacilli were found in the secretions obtained from bronchoscopy. Tubercle bacilli were recovered readily, even in the early stages of silicosis; in 89 per cent of the cases of tuberculosis with simple nodular silicosis and in 84 per cent of those with coalescent and conglomerate forms, the sputum was positive for acid-fast bacilli on examination of a stained smear.

Hematologic studies: The hemoglobin and erythrocyte counts were generally

high except in chronic advanced tuberculosis; in 68 per cent of the cases hemoglobin was above 12 gm., and in 62 per cent the red count was more than 4 million per cu. mm. Leukocytosis was uncommon, although 32 per cent showed a white count of more than 10,000 per cu. mm.

Miscellaneous determinations: Significant findings in the urine were noted in 32 patients (33 per cent) as follows: Varying amounts of albumin occurred in 18, sugar in 2, pus in 8, casts in 4; and 23 patients showed inability to concentrate the urine. An elevated blood urea nitrogen (more than 20 mg. per 100 ml.) was found in only 3 cases. A curious finding was the relatively low fasting blood sugar in 50 per cent of the series, with a level below 80 mg. per 100 ml. of blood. A wide variation of blood protein levels was also noted; and a reversal of the albumin-globulin ratio occurred in 2 cases. A negative serologic test for syphilis was present in all but 2 cases. The erythrocyte sedimentation rate was elevated in 65 cases, the average rate being 66 mm. drop in one hour.

The cutaneous reaction to tuberculin was positive with first- and second-strength purified protein derivative in all but 2 of the 54 miners tested; in 72 per cent a positive reaction was obtained on the first-strength test. In 7 patients with healed tuberculous lesions and in 8 with lesions classified as possibly active, a positive tuberculin test was also noted.

Roentgenographic Findings

The roentgenographic findings in the 750 cases of silicosis are summarized in tables 6 and 7. Classification of silicosis was based on a modification of the system proposed by the Committee on Pneumoconiosis of the American Public Health Association (18) in which the size of the nodulation on the roentgenogram determined the stage. With nodules up to 2 mm. in diameter, the classification of first stage was used; nodules up to 5 mm. indicated second stage; and larger nodules typified third stage, especially when coalescence or conglomeration were present. The so-called linear or granular phases were classed as borderline silicosis.

Presence of tuberculosis: The presence of tuberculosis frequently made the classification of silicosis into stages difficult, since it was often impossible to differentiate between the silicosis and the tuberculous infiltration. It is noted that the majority of cases of proved tuberculosis (88 per cent) were associated with the third stage of silicosis, the coalescent nodular phase being present in 50 per cent of the cases and the conglomerate phase in 29 per cent. While the diagnosis of advanced tuberculosis was usually definite, the determination of minimal tuberculosis has aroused questions of accuracy, due to the masking of the infection with the extensive nodulation of silicosis. It appeared that 7 cases of tuberculosis (7.2 per cent) were minimal, 21 cases (21.6 per cent) were moderately advanced, and 69 (71.2 per cent) were far advanced. Tuberculosis was unilateral in 74 cases and bilateral in 17. The upper lobes were most commonly involved. In the unilateral disease the right lobe was affected in 43 cases, while the left upper lobe was invaded in 11 instances. Various combinations of the lobes and different sites were noted; as for example, basal involvement oc-

curred in 15 cases, both unilateral and bilaterally. Localization of the tuberculosis was impossible in 5 cases, although the sputum contained tubercle bacilli.

TABLE 6

SILICOTIC MINERS AND THOSE WITH PROVED TUBERCULOSIS, CLASSIFIED BY STAGE OF ANTHRACOSILICOSIS AS SHOWN BY ROENTGENOGRAPHIC FINDINGS

STAGE OF ANTHRACOSILICOSIS	SILICOTIC MINERS		MINERS WITH PROVED TUBERCULOSIS		
	Number	Per cent distribution	Active	Healed	Suspected
All stages	750	100.0	97	7	8
Normal	20	2.7	1	—	—
Borderline	44	5.9	—	1	—
First stage	69	9.2	1	2	1
Nodular	39	5.2	1	2	1
Linear	30	4.0	—	—	—
Second stage	136	18.1	8	2	1
Nodular	110	14.6	8	2	1
Linear	26	3.5	—	—	—
Third stage	478	63.7	85	2	6
Nodular	43	5.7	8	2	—
Coalescent nodular	191	25.5	49	—	2
Conglomerate	244	32.5	28	—	4
No roentgenogram	3	0.4	2	—	—

TABLE 7

SILICOTIC MINERS AND THOSE WITH PROVED TUBERCULOSIS, CLASSIFIED BY ROENTGENOGRAPHIC FINDINGS

ROENTGENOGRAPHIC FINDINGS	SILICOTIC MINERS IN STUDY		MINERS WITH PROVED TUBERCULOSIS	
	Number	Per cent distribution	Number	Per cent of total
All findings	750	100.0	97	12.9
Asymmetrical lesions	320	42.7	83	25.9
Deviation of the trachea	199	26.5	50	25.1
Cavitation	75	10.0	66	88.0

Cavitation: Cavities were detected in 75 cases (10.0 per cent), of which 9 were not due to tuberculosis. In the 66 patients with proved tuberculosis, the majority of cavities were unilateral and single with one-half displaying a shifting fluid level. Cavitation was multiple in one lung in 11 patients and bilateral in 14 patients. In the 9 patients with nontuberculous cavities, carcinoma was found

in 2 instances, nonspecific pneumonitis in 2, and suspected tuberculosis in 5 instances.

It is recognized that tuberculosis will produce changes in the size and appearance of the silicotic nodules. A conspicuous feature is the development of shadows with fluffy and indistinct outline, with rapid growth and ultimate coalescence leading to massive conglomeration. It is assumed by some observers that the conglomeration almost always represents an associated tuberculous infection. In the 244 cases with conglomeration in the present study, however, the diagnosis of tuberculosis was made in only 28 instances (11.5 per cent).

Asymmetry of shadows: Asymmetry of shadows noted in the roentgenogram is an important criterion for the diagnosis of tuberculosis, reflecting the presence of localized infection. This phenomenon was noted in 320 cases (42.7 per cent) of the total group (750 cases) studied. Of this group of 320 cases, proved tuberculosis was present in only 25.9 per cent. The preponderant density corresponded with the site of tuberculosis. In the group of 97 proved tuberculous cases, asymmetry was present in 85.5 per cent.

Deviation of trachea: Deviation of the trachea is frequently considered to be the result of tuberculosis. This is based on the idea that, since simple silicosis is a bilateral symmetrical disease, the trachea remains in the mid-line. With tuberculosis involving one lung, producing asymmetry, the trachea is deviated toward the affected side. While deviation of the trachea occurred in 26.5 per cent of the total group (750 cases), only one-fourth of these were associated with tuberculosis. In the group of 97 proved cases of tuberculosis, deviation was present in 51.6 per cent, the shift being to the right in 44 cases.

Diaphragmatic motion: Restricted motion of the diaphragm was present in all but 2.7 per cent of the group. With extreme emphysema the diaphragm was lowered, flattened, and the movements markedly restricted.

Bronchoscopic Findings

Eighty-five patients with suspected tuberculosis or new growth were studied bronchoscopically. The findings in the tuberculosis-suspect group disclosed various degrees of chronic inflammation of the mucous membrane. In 5 patients with sputum negative for tubercle bacilli on routine studies, the bronchoscopic secretions revealed acid-fast bacilli, thus establishing the diagnosis of tuberculosis. In 3 patients with bronchial stenosis, granulomatous change, and laryngeal involvement, respectively, no acid-fast bacilli were found during hospitalization, but sputum positive for tubercle bacilli was obtained subsequently. In 12 instances the bronchoscopic findings and the presence of neoplastic cells in the bronchial secretions established the diagnosis of bronchogenic carcinoma.

DISCUSSION

The data in the present study indicate that tuberculosis complicating anthracosilicosis, with various degrees of disability, was suspected in approximately two-thirds of the patients on the basis of the past history or clinical features at

time of admission (table 8). The diagnosis of tuberculosis in the remaining one-third of the group was based on the discovery of acid-fast bacilli during routine examination of the sputum. In this latter group, 25 of the 33 tuberculous infections were detected at time of first admission, 2 on the second admission and 6 at the White Haven Sanatorium, where the patients had been transferred for special treatment of their respiratory impairment. It appears evident, therefore, that routine procedures will establish the diagnosis of tuberculosis.

Further analysis of table 5 shows that the diagnosis of tuberculosis may readily be established in 85 per cent of cases by simple examination of stained specimens of sputum. This is at variance with the view that the sputum often remains negative for tubercle bacilli until late in the disease, supposedly due to the intense fibrosis present and the infrequency of ulceration into the bronchi.

The prevalence of tuberculosis in silicosis in relation to the age of the coal miner, as disclosed in this study of disabled cases, is interesting and remarkable. As noted in figure 3, the prevalence was highest (approximately eight times the

TABLE 8

SILICOTIC MINERS WITH PROVED TUBERCULOSIS CLASSIFIED BY BASIS FOR DIAGNOSIS OF TUBERCULOSIS

BASIS FOR DIAGNOSIS OF TUBERCULOSIS	SILICOTIC MINERS WITH PROVED TUBERCULOSIS	
	Number	Per cent distribution
Total	97	100.0
Routine sputum studies	33	34.0
Physical examinations	32	33.0
History of proved tuberculosis prior to admission	22	22.7
Symptoms	10	10.3

normal rate) in the age group 35 to 44, and lowest (approximately equal to the general population) in those more than 55 years of age. These figures are at variance with the report of the Public Health Service (16), which indicates that the prevalence of tuberculosis among hard coal miners in the age group 35 to 44 is approximately twice, and in ages above 55 is approximately ten times, the rate for the general population. It should be emphasized, however, in clarifying the significance of the present data, that the findings are based on the study of miners who, in 85 per cent of the cases, were sufficiently disabled to have discontinued work before hospitalization. In contrast, the previous analysis of the Public Health Service was based on a large group of miners who had been working at the time of their examination. In addition the present statistics were based on the discovery of tubercle bacilli in the sputum, while in the previous study the diagnosis was arbitrary, based chiefly on the roentgenographic findings. It should also be mentioned in critical analysis that tuberculosis is being discovered with increasing frequency in the fourth and fifth decades, which in a

sense presents parallel figures with the present study. Indeed, it might be suggested that age in itself may have been a predisposing factor in certain cases of tuberculosis. Moreover, the low incidence of tuberculosis in the lower age group (less than 35 years of age), as recorded in the present study, admittedly may not be a clear indication of the frequency because the majority of miners admitted were of the third, fourth, and fifth decades.

While it appears that the prevalence of tuberculosis in silicosis relates primarily to the effects of silica, the important influences of environment should not be disregarded. The home conditions of miners as a whole, the overcrowding and privation, and the background or "soil" for dissemination and propagation of the infection should be recognized. Accordingly, it would be expected that members of the households of coal miners would show a higher incidence of tuberculosis than the general population. Nevertheless, mass roentgenographic surveys of 134,775 school children, foodhandlers, industrial workers, and various community groups in the anthracite regions of Pennsylvania during 1948 to 1950 have revealed an incidence of reinfection-type tuberculosis of only 0.09 per cent. In addition, a review of the case histories of tuberculous miners admitted to the White Haven Sanatorium for the past twenty years has not revealed a high incidence of tuberculosis among the immediate families. These figures appear incongruous and yet surprising when the mortality rate from tuberculosis for the counties of the anthracite region of Pennsylvania is analyzed. For example, in Luzerne County, where most of the coal miners admitted to White Haven live, the average death rate from tuberculosis for the years 1939 to 1946 was only 42 per 100,000. Likewise, the rates for the other counties range from 31 in Carbon County to 46 in Lackawanna County. It is interesting that the figures for 1948 are lower, i.e., 30.7 for Luzerne County, 9.2 for Carbon County, and 33.6 for Lackawanna County, respectively. Indeed, it is difficult to reconcile the low incidence and mortality rates with the figures disclosed in the present study. This poses the pertinent question whether tuberculosis may have been masked by the bizarre developments of silicosis.

The data indicate that the prevalence of tuberculosis bears some relation to the length of exposure to silica and the extent of the resulting silicosis. The unanswered questions relate to the reactivation of quiescent tuberculous foci and the development of a new infection resulting from the inhalation of tubercle bacilli from the mines or elsewhere. It is known that silica exerts a definite chemical attraction to calcium and it may be conjectured that decalcification of healed primary foci may occur with subsequent endogenous reinfection. No roentgenographic or pathologic confirmation of this has been found and it seems likely, therefore, that the most probable course of events is that of a fresh infection, exogenous in nature, occurring in a lung already damaged by silica. Recently, however, Sander (19) has indicated that the deleterious effects of silicosis on tuberculosis are largely on pre-existing tuberculous foci and are relatively infrequent as a predisposing factor to new tuberculosis. This may suggest that the coal miners in the present study were infected with tuberculosis prior to their employment, their disease being aggravated by exposure to silica.

With reference to the development of a new tuberculous infection, it should be mentioned that the practice of expectoration in the mines is not uncommon. It would appear that the deposition of tubercle bacilli in the dust for subsequent inhalation provides the background for new infection. Indeed, neither tissue sensitivity reactions due to silicosis nor the exposure to tuberculosis can be disregarded.

The clinical features presented by the anthracosilicotic coal miner with complicating tuberculosis are typical, but the onset may be obscure. It is known that cough, dyspnea, weakness, weight loss, and other complaints (in varying degrees) are present for years in nontuberculous cases, depending on the extent of fibrosis and the degree of emphysema. The most striking feature of definite activity is the rapid and continued aggravation of existing symptoms. The lack of clinical activity in some cases has been explained on the basis of the high degree of fibrosis which tends to hold the infection in abeyance and prevents or retards absorption of the toxic products of tuberculosis. In such instances the physical signs, roentgenograms, and episodes of cough, expectoration, and weakness must be carefully followed.

Case Reports

The following cases illustrate the aspects of silicosis that require elucidation in the absence of tubercle bacilli in the sputum:

Case 1. P. K., a 57-year-old miner with a history of thirty-eight years of underground exposure, had stopped work one year prior to admission because of progressive dyspnea and frequent "chest colds." Physical examination revealed bronchovesicular breath sounds and many medium coarse rales over the right upper lobe, and the roentgenogram disclosed a coalescent nodular infiltration throughout both lung fields, especially in the upper portions. The condition was classified as third-stage anthracosilicosis with probable tuberculosis in the upper lobe of the right lung. Since the sputum examinations were negative for tubercle bacilli, the miner was discharged for subsequent observation. With readmission eight months later, the moist rales were present and the sputum negative for tubercle bacilli. A bronchogram with lipiodol revealed extensive saccular and cylindrical bronchiectasis of the right upper and middle lobes (figure 4).

This case emphasizes that, when laboratory confirmation is not readily forthcoming, other causes for physical findings typical of tuberculosis must be considered.

Case 2. J. C., a 55-year-old coal miner with a history of thirty-six years of underground exposure to silica dust, had stopped work three months prior to admission because of progressive dyspnea associated with a "chest cold," marked cough, expectoration, weakness, and weight loss of 23 pounds. There were no rales on examination of the chest. Roentgenograms of the chest revealed large areas of conglomerate fibrosis in both mid-lung regions, with a small cavity in the right apex, features considered to be characteristic of third-stage anthracosilicosis with suspected tuberculosis. Nevertheless, the sputum remained persistently negative for tubercle bacilli. On readmission of the patient six months later, a marked extension of the process in the right upper lobe was revealed with accentuation of the cavitation and sputum positive for tubercle bacilli (figure 5).

FIG. 4. Case 1 (patient P. K.). Roentgenograms showing third stage anthracosilicosis (left) and bronchiectasis in the right upper and middle lobes (right). Tuberculosis had been suspected on the basis of the physical signs in the right upper lobe.

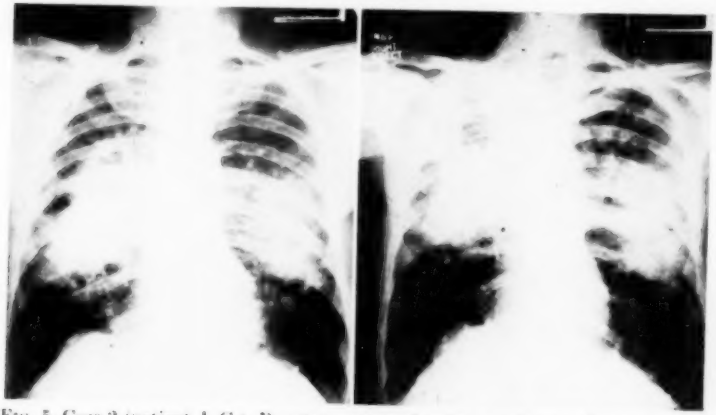

FIG. 5. Case 2 (patient J. C.). Roentgenograms showing massive conglomerate anthracosilicosis (left) and marked extension of the tuberculous process in the right upper lobe six months later (right).

This case illustrates the ultimate outcome of a considerable number of conglomerate lesions and emphasizes the necessity for close observation of all cases of suspected tuberculosis, especially where cavitation is present.

Case 3. J. Y., a 63-year-old miner with a thirty-eight-year history of exposure, had been disabled for the past eighteen years because of progressive dyspnea. Approximately one

year before entry there was an increase of cough and expectoration with progressive weakness but no loss of weight or hemoptysis. Roentgenograms of the chest revealed a diffuse coalescent nodular infiltration throughout, with dense infiltration in the right mid-lung area where a moderate-sized cavity and shifting fluid level were noted (figure 6). While tuberculosis was suspected, the sputum remained persistently negative for tubercle bacilli

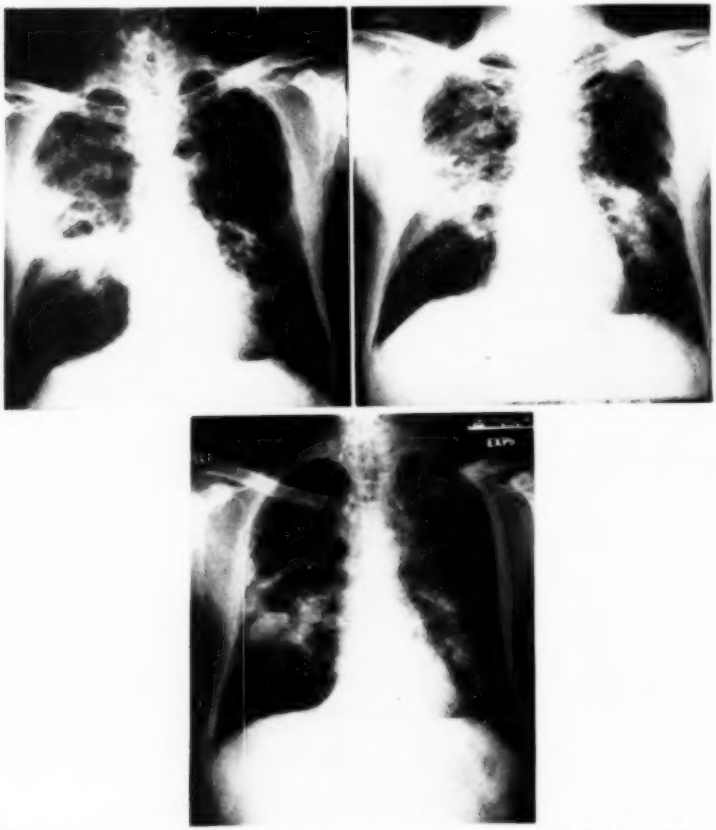

FIG. 6. Case 3 (patient J. Y.). Roentgenograms showing cavity and fluid level in right mid-lung area (upper left), disappearance of fluid level after intermittent positive pressure breathing (upper right), and reappearance three months later (bottom).

on stained smears, concentrates, gastric secretions, and culture. Pulmonary function studies indicated a marked degree of emphysema. The patient received a course of intermittent positive pressure breathing treatments, with considerable symptomatic improvement but no sustained change in physiologic function. It was noted, however, that the fluid level had disappeared, indicating emptying of the cavity. On readmission three months later, the fluid level was again visible and the sputum remained negative for tubercle bacilli.

Bronchoscopic examination yielded secretions which contained acid-fast bacilli, and the diagnosis was established.

This case emphasizes the value of a persistent search for tubercle bacilli where cavitation is present, since it has been shown at autopsy that the walls of the cavity may contain bacilli although they may not readily be recovered in the sputum.

Case 4. F. S., a 45-year-old miner with a history of only twelve years of underground exposure to silicosis, stopped work in 1930 because of an injury to his leg. He was admitted to the hospital on January 15, 1948 with the chief complaints of dyspnea during effort, moderate cough, and expectoration. The physical examination was essentially normal. Roentgenograms revealed scattered areas of coalescent nodular infiltration, more pronounced in the right mid-lung area, with the general features of third-stage anthracosilicosis. A severe hemoptysis occurred on the day of admission, followed by an elevation of temperature. Subsequent roentgenograms revealed a marked increase in the infiltration in the right mid-lung area, suggesting tuberculosis. However, the sputum remained persistently negative for tubercle bacilli, and penicillin administration was employed. The temperature promptly returned to normal and a roentgenogram disclosed remarkable improvement of the right lung (figure 7).

This case illustrates the behavior of intercurrent pulmonary infection in cases of silicosis. While tuberculosis should be regarded as the most likely etiologic factor, the persistent failure to recover tubercle bacilli from the sputum emphasized the need to consider other possibilities.

Prognosis: The life expectancy of silicosis with complicating tuberculosis treated at home is two or three years. As noted in the present survey, 42 miners were dead within two years of the diagnosis, and 47 died within three years after entry in the hospital (table 9). With sanatorium care, as employed at White Haven, life expectancy in some cases may be increased to four years or more, even in patients who continue to discharge tubercle bacilli in the sputum. It is believed that superimposed intercurrent infection with bronchiolar blockage is an important factor in reducing the span of life.

The extent and type of silicosis in which tuberculosis is a complication bears a definite relationship to the course of the disease (table 10). Longevity is somewhat more promising in the nodular stage than in the conglomerate stage. This differs with the findings of Dayman (20) who reported no correlation between the size and number of silicotic nodules determined by the roentgenogram and the course leading to a fatal termination from tuberculosis.

Treatment: Treatment of anthracosilicosis complicated by tuberculosis is limited chiefly to symptomatic relief. Strict rest in bed should be employed only in advanced cases with toxemia; lying flat in bed for periods of eight to sixteen hours daily with bathroom privileges and sitting in a chair three to four hours daily is more effective than a strict bed-rest regimen. The use of narcotic drugs to control cough is not recommended because of their tendency to cause retention of bronchial secretions. Antispasmodic drugs such as ephedrine and expectorants are disappointing. The usual procedures of collapse therapy are not applicable since the silicotic fibrosis impairs pulmonary function and interferes with relaxation or contraction of the lung, sometimes leading to spontaneous

pneumothorax and retained bronchial secretions. Cavity closure is seldom obtained, either by artificial pneumothorax or thoracoplasty, except in cases with early nodular silicosis. Pneumothorax was induced in 3 patients in the present series with minimal silicosis, but in each instance extensive adhesions appeared

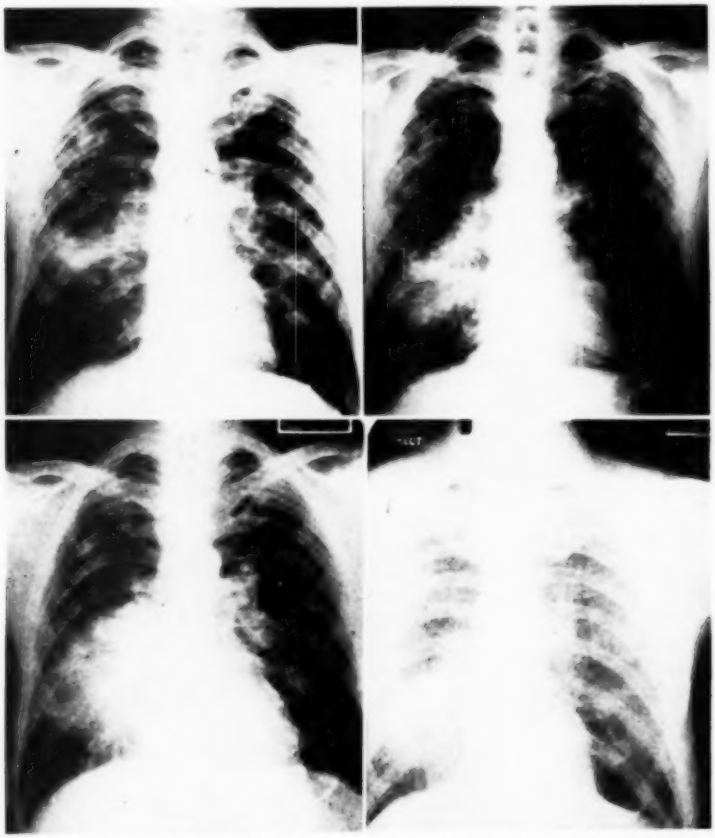

FIG. 7. Case 4 (patient F. S.). Roentgenograms showing coalescent nodular anthracosilicosis on admission (upper left), an area of nontuberculous pneumonitis in the right mid-lung area two weeks later (upper right), further spread of the pneumonitis a week later (lower left), and partial resolution one month after admission (lower right).

and the procedure was abandoned. In one of these patients, thoracoplasty was employed successfully with closure of the cavity and "conversion" of the sputum.

This experience with pneumothorax is in contrast with the results in localized fibrosis of tuberculosis, where the lung retains a certain degree of contractility

or is easily compressible, a favorable mechanism for selective collapse. Excision surgery usually is not favorable due to the reduced pulmonary reserve. Extrapleural pneumothorax has been advocated for treatment and as a test of respiratory reserve, but the results have not been encouraging (21). Pneumoperitoneum provides symptomatic relief through reduction of residual air, but the influence

TABLE 9

SILICOTIC MINERS WITH PROVED TUBERCULOSIS AND DEATHS AMONG THEIR NUMBER, CLASSIFIED BY YEAR DIAGNOSED

YEAR DIAGNOSED*	SILICOTIC MINERS WITH PROVED TUBERCULOSIS			
	Total	Deaths after diagnosis of tuberculosis		
		First year	Second year	Third year
Total	97	28	14	5
1947–1948	32	9	10	5
1948–1949	30	14	3	—
1949–1950	17	5	1	—
1950–1951	18	—	—	—

* Fiscal year.

TABLE 10

SILICOTIC MINERS WITH PROVED TUBERCULOSIS, DEATHS AMONG THEIR NUMBER, AND AVERAGE PERIOD OF SURVIVAL OF THOSE WHO DIED, CLASSIFIED BY STAGE OF SILICOSIS

STAGE OF SILICOSIS	SILICOTIC MINERS WITH PROVED TUBERCULOSIS		
	Total	Deaths	Average period of survival in months of those who died
All stages	97	47	*
Normal or borderline	1	—	—
First stage	1	—	—
Second stage	8	3	21
Third stage	85	44	*
Nodular	8	1	9
Coalescent nodular	49	27	11.8
Conglomerate	28	16	10.2
No roentgenogram	2	—	—

* Data not available.

on the tuberculous process is limited. Streptomycin and para-aminosalicylic acid have been used extensively at White Haven but were effective only in reducing the manifestations of toxemia. Terramycin (250 mg. every six hours for twelve doses) is valuable for controlling bouts of intercurrent infections.

Studies of uncomplicated anthracosilicosis (22, 23) indicate that spasm and

blockage of bronchioles are important factors in the cause of pulmonary symptoms. The use of intermittent positive pressure breathing therapy with 100 per cent oxygen and nebulization of bronchodilator drugs have been employed guardedly in a selected group of 12 patients with silicosis and complicating tuberculosis (24). Certain value has been noted in the control of racking cough, paroxysmal dyspnea, and difficult expectoration. This is accomplished through reduction of bronchospasm, favoring increased alveolar aeration and improvement in bronchial drainage. There has been no objective evidence that the tuberculosis or silicosis were influenced structurally.

SUMMARY

The clinical features of tuberculosis complicating anthracosilicosis in an unselected group of 637 disabled and 113 non-disabled hard coal miners are presented.

The diagnosis of active reinfection type of pulmonary tuberculosis was established in 97 patients (12.9 per cent); the diagnosis of inactive or healed tuberculosis was made in 7 additional patients (0.9 per cent); and in 8 patients (1.1 per cent) the lesions were classified as probably tuberculous.

Diagnosis of the proved cases of tuberculosis was made on the basis of sputum positive for tubercle bacilli; in 85 per cent of the patients the bacilli were detected on examination of a stained smear of sputum.

The presence of tuberculosis was predicted in two-thirds of the patients on the basis of history, physical signs, and symptoms at time of admission; the disease was not suspected in one-third of the patients.

The data indicate that complicating tuberculosis should be suspected in the presence of anthracosilicosis when the symptoms are abrupt in onset and become progressively exaggerated, when localized moist rales are present, and when the roentgenogram reveals asymmetry, coalescence, or cavitation; in most instances combinations of these findings were present.

A definite correlation exists between the prevalence of tuberculosis and the age of the coal miner, the length of exposure, and the extent of the anthracosilicosis.

Tuberculosis complicating anthracosilicosis is most prevalent during the fourth and fifth decades of life; in the age group 35 to 44, it is approximately 8 times more frequent than in the general population; in the age group 45 to 54, approximately 3 times more frequent; and in the age groups 55 or older, approximately equal in frequency.

Tuberculosis is most commonly associated with third-stage silicosis. It appears that silicosis in hard coal miners predisposes to the development of tuberculosis but the incidence of active disease is lower than is generally suggested; the probable prevalence of the disease may be 12 to 15 per cent rather than the extremes of 3 to 75 per cent, as suggested in the literature.

The prognosis of tuberculosis complicating silicosis is poor; approximately two-thirds of the patients die within three years after the development of manifest tuberculosis; sanatorium care may prolong life in selected cases.

Treatment is essentially symptomatic; when functional impairment of the bronchioles and alveoli is a major factor, the guarded use of intermittent positive pressure breathing with nebulization of antimicrobial and bronchodilator drugs provides symptomatic relief.

SUMARIO

La Tuberculosis en la Antracosilicosis

Preséntanse aquí las características clínicas de la tuberculosis como complicación de la antracosilicosis en un grupo no seleccionado de 637 mineros de carbón duro incapacitados y 113 sin incapacitar.

El diagnóstico de tuberculosis pulmonar tipo de reinfección activa fué establecido en 97 casos (12.9 por ciento); en 7 casos más (0.9 por ciento) se diagnosticó tuberculosis inactiva o cicatrizada; y 8 casos (1.1 por ciento) fueron clasificados como probablemente tuberculosos.

El diagnóstico de los casos comprobados de tuberculosis se hizo a base de esputo positivo; en 85 por ciento se encontraron bacilos en el frote directo simple.

La presencia de tuberculosis fué predicha en dos terceras partes de los casos a base de la historia, signos físicos y síntomas en la fecha de ingreso; en la otra tercera parte no se sospechó la existencia del mal.

Los datos indican que debe sospecharse la presencia de tuberculosis como complicación si los síntomas muestran iniciación súbita y se exageran cada vez más, si hay estertores húmedos localizados y si las radiografías revelan coalescencia asimétrica o cavernas; en la mayor parte de los casos existían combinaciones de esas pautas.

Existe correlación bien definida entre la frecuencia de la tuberculosis y la edad del minero de carbón, la duración de la exposición y la extensión de la antracosilicosis.

La tuberculosis como complicación de la antracosilicosis abunda más durante el cuarto y el quinto decenios de la vida; a la edad de 35 a 44 años, alcanza una difusión aproximadamente ocho veces mayor que en la población general; a la edad de 45 a 54, aproximadamente el triple; y más allá de los 55 años, aproximadamente igual.

La tuberculosis se asocia más comúnmente con el período terciario de la silicosis. Parece que la silicosis en los mineros de carbón duro predispone a la aparición de la tuberculosis, pero la incidencia de enfermedad activa es menor de lo indicado generalmente; el coeficiente probable de la dolencia puede ser de 12 a 15 por ciento, según sugiere la literatura.

El pronóstico de la tuberculosis que complica la silicosis es malo; aproximadamente dos terceras partes de los enfermos mueren en término de tres años de la aparición de tuberculosis manifiesta; la asistencia sanatorial puede prolongar la vida en casos seleccionados.

El tratamiento es esencialmente sintomático; cuando la disfunción de los bronquiolos y alvéolos constituye un factor principal, el uso cauteloso de la respiración con presión positiva intermitente unido a la nebulización de antibióticos y de drogas broncodilatadoras proporciona alivio sintomático.

RESUME

La tuberculose dans l'anthracosilicose

Les caractères cliniques de la tuberculose compliquant l'anthracosilicose dans un groupe, non sélectionné de mineurs travaillant dans les houillères, composé de 637 mineurs frappés d'incapacité et de 113 mineurs non frappés d'incapacité, sont décrits.

Le diagnostic du type de réinfection évolutive a été établi dans 97 cas (12,9%); le diagnostic de tuberculose non active ou guérie a été fait dans 7 autres cas (0,9%); 8 cas (1,1%) ont été classés comme tuberculose probable.

La confirmation du diagnostic de tuberculose a été établi sur la base de crachats positifs; dans 85% des cas les bacilles étaient recouvrés sur simple étalement direct.

La présence de la tuberculose a été affirmée dans deux tiers des cas d'après l'histoire de la maladie, les signes physiques et les symptômes présentés au moment de l'admission. La maladie n'était pas soupçonnée dans un tiers des cas.

Les données montrent que la tuberculose est une complication à envisager quand les symptômes débutent brusquement et s'exagèrent progressivement, en présence de râles humides, ou lorsque les radiographies montrent une asymétrie des adhérences ou des cavernes; dans la plupart des cas observés, ces critères existaient.

Il existe une corrélation définie entre la prédominance de la tuberculose et l'âge du mineur, la durée de l'exposition aux poussières et l'importance de l'anthracosilicose.

La tuberculose comme complication de l'anthracosilicose atteint son maximum de fréquence pendant la période de quarante à soixante ans; entre 35 et 44 ans sa prédominance est approximativement huit fois plus grande que dans la population globale; entre 45 et 54 ans, elle est approximativement trois fois plus grande; au-dessus de 55 ans, elle est sensiblement égale.

La tuberculose est le plus souvent associée au troisième stade de la silicose. Il semble que la silicose du mineur de houillères prédispose au développement de la tuberculose, mais l'incidence de l'affection évolutive est habituellement moins élevée que celle qui est généralement indiquée; selon l'article, le taux probable de la tuberculose serait de 12 à 15%.

Le pronostic de la tuberculose associée à la silicose est mauvais; environ deux tiers des malades succombent dans les trois ans qui suivent l'apparition des signes de tuberculose en activité. Les soins en sanatorium peuvent prolonger la durée de la vie dans les cas sélectionnés.

Le traitement est essentiellement symptomatique; quand le facteur principal est constitué par un trouble de la fonction des bronchioles et des alvéoles, l'usage prudent de la méthode de respiration avec pression positive intermittente et nébulisation d'antibiotiques et de broncho-dilatateurs procure une amélioration fonctionnelle.

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EXPERIMENTAL TUBERCULOSIS[1, 2]

III. Further Observations on the Effects of Alteration of the Pulmonary Arterial Circulation on Tuberculosis in Monkeys

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(Received for publication June 29, 1951)

In previous studies in this laboratory, it has been shown (1, 2) that alterations of the pulmonary arterial circulation in monkeys infected intravenously with human tubercle bacilli produce profound changes in the character of the tuberculous process. It was found that anastomosis between systemic and pulmonary arteries results in an extensive caseous form of the disease in the lung on the side of the anastomosis. Subsequent experiments with ligation of a pulmonary artery in similarly infected animals demonstrated that the same type of caseous process develops in the lung on the side of the arterial ligation. In contrast, the lung on the side opposite the ligation or anastomosis shows the miliary[3] form of tuberculosis typically found in both lungs of control animals.

It should be emphasized that the same extensive caseous changes develop in the lungs of monkeys which undergo such widely different operative procedures as ligation of a pulmonary artery and anastomosis between a systemic and a pulmonary artery. These procedures appear to produce in the lung on the side of operation similar favorable conditions for progression of the disease.

In our previous studies of the effects of experimental alterations of the pulmonary circulation on tuberculosis (1, 2), variations in the arterial flow to the lungs were produced in monkeys under standardized conditions of exposure to infection. The route of administration and, in so far as possible, the dosage of tubercle bacilli were kept constant. As a subsequent phase of this investigation, it seemed desirable to study the effects of anastomosis between systemic and pulmonary arteries in monkeys under a variety of conditions of exposure to tubercle bacilli. This report presents these further observations and discusses their relation to the previous investigations.

METHODS

In these experiments, 31 healthy *Macaca mulatta* monkeys were used. All were selected from carefully segregated stock animals which had consistently shown negative reactions to repeated tuberculin tests.

All monkeys were submitted to thoracotomy. In the majority of these animals, an end-to-end anastomosis was carried out between systemic and pulmonary arteries. The in-

[1] From the Laboratory of Infectious Diseases of the National Institutes of Health, Bethesda, Maryland, and the Department of Surgery of the Johns Hopkins University School of Medicine, Baltimore, Maryland.

[2] This study was aided, in part, by a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.

[3] The term "miliary" is used throughout this report in a purely descriptive sense, indicating large numbers of uniformly distributed small tubercles.

nominate artery was anastomosed to the distal end of the right pulmonary artery in one group of animals; while in a smaller group of monkeys an end-to-end anastomosis was done between the innominate or left subclavian artery and the distal end of the descending trunk[4] of the right or left pulmonary artery. Simple thoracotomy was performed as a control in the remaining animals.

The standard dose of the same virulent strain of human tubercle bacilli which was used in the previously reported experiments (1, 2) was given intravenously to some of these animals after operation. Others received this standard dose of bacilli by subcutaneous injection after operation. Four monkeys received a much larger dose of tubercle bacilli by intravenous injection the day before operation, while another animal in this group was infected with the larger dose of bacilli by direct injection into the pulmonary artery at the time of operation. Finally, 6 uninfected monkeys were exposed after operation to infected animals in a "natural infection" experiment.

Bacteriologic Technique

A virulent strain of *Mycobacterium tuberculosis* var. *hominis* isolated by one of us (B. J. O.) at the National Institutes of Health was used in these experiments. The virulence of this strain, the details of culture, and the standardized technique employed in preparation of emulsions for animal inoculation have been discussed in a previous communication (1). The dose of tubercle bacilli given intravenously or subcutaneously to 20 monkeys in the present experiments consisted of 1 cc. of a suspension containing 10^{-4} mg. of organisms per cc. In 5 other monkeys a much larger dose was used: 1 cc. of a suspension containing 1 mg. of tubercle bacilli per cc. In the "natural infection" experiments, 6 monkeys were exposed to tuberculosis by confinement to individual cages in the same isolation room with other monkeys which had been infected by the intravenous or subcutaneous route with 10^{-4} mg. of the standard strain of virulent human tubercle bacilli.

Operative Technique

Intravenous sodium pentobarbital anesthesia (30 mg. per kg.) with morphine-atropine preoperative medication was used. Pulmonary ventilation was maintained by means of a mechanical respirator which delivered oxygen through an endotracheal tube (3). Aseptic surgical technique was used in all operations.

The chest was entered anteriorly through the fourth intercostal space on the left or right. The pulmonary artery to the exposed lung was dissected free. After the innominate artery on the right or the subclavian artery on the left had been isolated and occluded proximally with a rubber-shod clamp, it was ligated distally and divided. The adventitia was cleaned from the proximal end of the systemic artery before it was placed in apposition to the pulmonary artery.

The anastomosis was carried out following the technique of Blalock (4). In an end-to-end union between the innominate artery and the right pulmonary artery, the latter was ligated deep in the mediastinum near the main pulmonary trunk, occluded distally with a rubber-shod clamp, and divided between the ligature and the clamp. The proximal end of the innominate artery was then sutured to the distal end of the right pulmonary artery with a continuous everting mattress suture of 6-0 arterial silk on an atraumatic needle.

A similar technique was used in an end-to-end anastomosis between a sys-

[4] The term "descending trunk" will be used in this article to describe that portion of the right or left pulmonary artery immediately distal to the origin of the branches to the upper lobe. The descending trunk of a pulmonary artery supplies the middle and lower lobes of the lung.

temic artery and the descending trunk of a pulmonary artery. The proximal end of the systemic vessel was sutured to the end of the descending trunk of the pulmonary artery distal to the origin of the branch to the upper lobe. In operations of this type on the left side, the left subclavian artery was united to the descending trunk of the left pulmonary artery. In operations on the right side, the innominate artery was united to the descending trunk of the right pulmonary

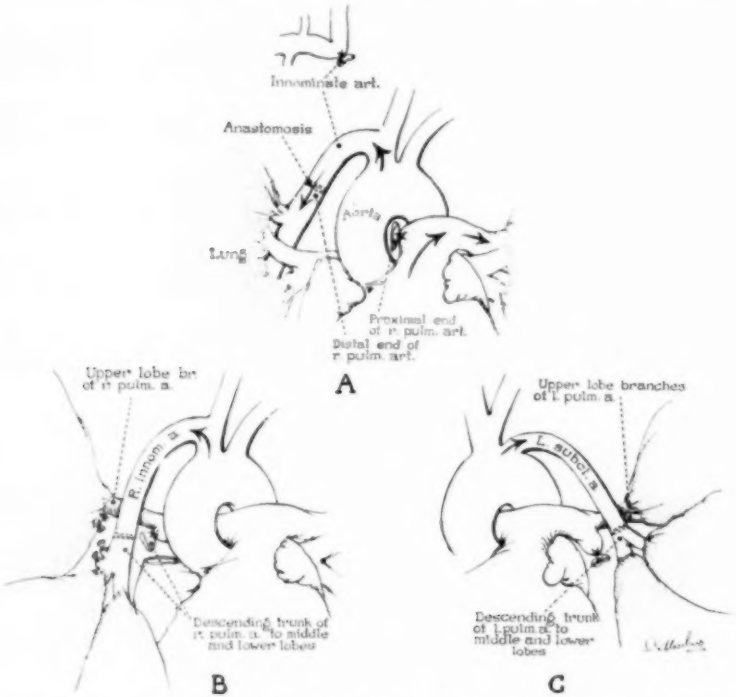
Innominate art.
Anastomosis
Aorta
Lung
Proximal end of r. pulm. art.
Distal end of r. pulm. art.
A
Upper lobe br. of r. pulm. a.
R. innom. a.
Descending trunk of r. pulm. a. to middle and lower lobes
B
Upper lobe branches of l. pulm. a.
L. subcl. a.
Descending trunk of l. pulm. a. to middle and lower lobes
C

FIG. 1. Types of anastomosis used in these experiments. A. Anastomosis between the end of the innominate artery and the end of the right pulmonary artery. B. Anastomosis between the innominate and the descending trunk of the right pulmonary artery. C. Anastomosis between the left subclavian artery and the descending trunk of the left pulmonary artery.

artery. In some of these operations the upper lobe branches of the pulmonary artery were ligated, while in others the upper lobe branches were left intact. Figure 1 illustrates the varieties of the anastomosis used in these experiments.

After completion of the anastomosis, the constricting devices were removed from the vessels and the mediastinal pleura was closed. The lung was carefully re-expanded and closure of the chest wall was carried out with interrupted fine silk sutures.

In control thoracotomy the chest was entered in the fourth intercostal space on the right or left; no anastomosis was performed. In these cases the lung was packed down with moist gauze for 15 to 60 minutes, after which it was carefully reinflated and closure of the chest wall was carried out.

Following operation each monkey received a single intramuscular injection of 300,000 units of penicillin in oil. The animals were kept in separate cages in the same isolation room and were fed stock diet until their deaths.

RESULTS

There were no immediate postoperative deaths in the 31 monkeys submitted to operation. All wounds healed per primam and there were no instances of wound infection or empyema. Tuberculosis developed and progressed to a fatal termination in all of the injected animals[5] and in 3 of the 6 animals comprising the natural infection experiment. A complete autopsy was performed immediately after death in each case. A special attempt was made to compare the character and extent of the tuberculous process in the lung or the lobes on the side of the systemic pulmonary anastomosis with the lesions in the other pulmonary units of the same animal and with the lesions in the lungs of the control animals. Sections were taken from the lungs and other viscera for microscopic study. Color photographs were made as an aid in recording gross pathologic appearances.

Systemic Pulmonary Anastomosis in Monkeys Infected Intravenously After Operation

In 5 monkeys an end-to-end anastomosis between the innominate artery and the right pulmonary artery was carried out. These animals were infected with the standard dose (10^{-4} mg.) of tubercle bacilli by intravenous injection 13 to 20 days after operation. The monkeys lived from 94 to 195 days after inoculation. Pertinent data for these animals are summarized in table 1. The arterial anastomosis was widely patent at autopsy in each of the 5 monkeys.

In all of the 5 monkeys the extent of the pulmonary disease as seen at autopsy was greater in the lung on the side of the systemic pulmonary anastomosis. Examples of this difference in the disease process are seen in figure 2. Numerous conglomerate caseous lesions were present in the lung on the side of the operation. This lung showed massive caseous areas in contrast to the opposite lung which presented smaller, scattered tubercles, usually of the miliary type. In most of the animals the lung on the side of the anastomosis was larger than the opposite lung. This increase in size of the lung seems to be largely due to the greater amount of caseous tuberculosis present.

Extrapulmonary lesions in these monkeys were limited to the liver, lymph nodes, and spleen. Figure 3 illustrates typical lesions present in liver and spleen.

[5] One monkey (I 86) which was scheduled to have an intravenous injection of 10^{-4} mg. of tubercle bacilli on May 31, 1950 showed no evidence of tuberculosis at autopsy on March 7, 1951. This apparently anomalous result can only be explained by the animal's ability to resist this dosage or by an unknown error by which this monkey did not receive the scheduled injection.

TABLE 1

EXPERIMENTAL DATA ON EFFECTS OF SYSTEMIC PULMONARY ANASTOMOSIS IN MONKEYS WITH VARIOUS MODES OF EXPOSURE TO TUBERCULOSIS

MONKEY NUMBER	OPERATIVE PROCEDURE	DOSAGE OF TUBERCLE BACILLI (NUMBER OF VIABLE PARTICLES)	SURVIVAL TIME AFTER EXPOSURE TO TUBERCLE BACILLI (DAYS)	DISTRIBUTION OF PULMONARY LESIONS AT AUTOPSY		
				Extensive Caseation in Lobes or Lung Supplied by the Anastomosis	More Extensive Elsewhere in Lungs	No Difference in Lobes or Lungs
Group Infected Intravenously (10⁻¹ Mg.) After Operation						
H 1	Anastomosis innominate to end of right pulmonary artery	99	129	++++ Right lung		
H 2	Anastomosis innominate to end of right pulmonary artery	99	94	+++ Right lung		
H 4	Anastomosis innominate to end of right pulmonary artery	99	118	+++ Right lung		
H 15	Anastomosis innominate to end of right pulmonary artery	99	124	++++ Right lung		
H 16	Anastomosis innominate to end of right pulmonary artery	99	195	+++ Right lung		
I 75	Anastomosis innominate to end of descending trunk of right pulmonary artery	47	110	++ Right middle and lower lobes		
I 77	Anastomosis innominate to end of descending trunk of right pulmonary artery	47	100	++++ Right middle and lower lobes		
I 85	Anastomosis innominate to end of descending trunk of right pulmonary artery	47	135	++++ Right lung		
I 86	Anastomosis innominate to end of descending trunk of right pulmonary artery	47	280			No gross TB
I 73	Anastomosis left subclavian to end of descending trunk of left pulmonary artery	47	70	+ Left middle and lower lobes		
I 74	Anastomosis left subclavian to end of descending trunk of left pulmonary artery	47	117	++++ Left lung		
I 76	Control thoracotomy, right	47	280			Miliary
H 6	Control thoracotomy, right	99	118			Miliary
H 42	Control thoracotomy, left	387	91			Miliary
H 43	Control thoracotomy, left	387	150			Miliary

Group Infected Subcutaneously (10^{-4} Mg.) After Operation						
H 5	Anastomosis innominate to end of right pulmonary artery	99	144	+ Right lung		
H 7	Anastomosis innominate to end of right pulmonary artery	99	161	+ Right lung		
H 8	Anastomosis innominate to end of right pulmonary artery	99	378		+ Left lung	
H 3	Control thoracotomy, right	99	128			Miliary
H 10	Control thoracotomy, right	99	352			Miliary
Group Exposed to "Natural Infection" After Operation						
CA 57	Anastomosis innominate to end of right pulmonary artery	—	391	++++ Right lung		
CA 55	Anastomosis innominate to end of right pulmonary artery	—	Still alive (600+)			
CA 62	Anastomosis innominate to end of right pulmonary artery	—	648			No gross TB
CA 74	Anastomosis innominate to end of right pulmonary artery	—	Still alive (600+)			
CA 70	Control thoracotomy, right	—	221			Miliary
CA 44	Control thoracotomy, right	—	622			No gross TB
Group Infected Intravenously with Large Dose of Bacilli (1 Mg.) Before Operation*						
106	Anastomosis left subclavian to end of left pulmonary artery	1,000,000	27	++++ Left lung		
23	Anastomosis innominate to end of right pulmonary artery	11,400,000	21	++ Right lung		
C 18	Anastomosis left subclavian to end of left pulmonary artery	2,450,000	19			Miliary
C 24	Anastomosis left subclavian to end of descending trunk of left pulmonary artery	2,465,000	27	++ Left middle and lower lobes		
C 17	Anastomosis left subclavian to end of descending trunk of left pulmonary artery	8,550,000	17			Miliary

* One monkey in this group (No. 106) was infected at the time of operation by direct injection into the pulmonary arteries.

Microscopic study of sections from the lung and other viscera demonstrated numerous tubercle bacilli and confirmed the gross findings.

Systemic Pulmonary Anastomosis in Monkeys Infected Subcutaneously After Operation

In 3 monkeys an end-to-end anastomosis between the innominate artery and the right pulmonary artery was performed. The animals were infected with the

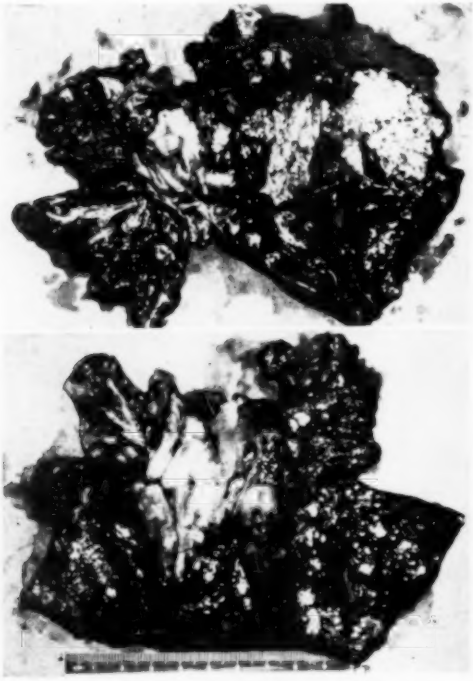

FIG. 2. (Monkeys H 15 and H 16). Anastomosis between innominate and right pulmonary artery in two monkeys infected by intravenous injection of 10^{-4} mg. of tubercle bacilli after operation. Dorsal views of sectioned lungs at autopsy, showing confluent caseous lesions in right lung in each instance.

standard dose (10^{-4} mg.) of tubercle bacilli by subcutaneous injection 13 days after operation. The monkeys lived 144, 161, and 378 days after inoculation. At autopsy the anastomosis was found to be widely patent in each animal.

In these 3 monkeys, at autopsy scattered caseonodular lesions were found in the lungs. In 2 of the 3 animals these caseous lesions were on the side of the systemic pulmonary anastomosis; however, in one of these 2, there were more numerous miliary lesions in the contralateral lung (figure 4). In the third animal

similar caseonodular lesions were found in the lung contralateral to the anastomosis. The predominance of caseous tuberculosis on the side of the anastomosis was considerably less striking than in the animals infected intravenously.

FIG. 3. (Monkey H 15). Anastomosis between innominate and right pulmonary artery in monkey infected by intravenous injection of 10^{-4} mg. of tubercle bacilli after operation. Photograph of abdominal viscera at autopsy.

FIG. 4. (Monkey H 7). Anastomosis between innominate and right pulmonary artery in monkey infected by subcutaneous injection of 10^{-4} mg. of tubercle bacilli after operation. Dorsal view of sectioned lungs, showing a few caseous lesions in right lung.

Extrapulmonary lesions were similar to those encountered in the animals infected intravenously. Microscopic study of sections from the lungs and other viscera confirmed the gross findings at autopsy.

Systemic Pulmonary Anastomosis in Monkeys with "Natural Infection" After Operation

In 4 monkeys, an end-to-end anastomosis was performed between the innominate artery and the right pulmonary artery. Three weeks after operation these animals were placed in individual cages in the same isolation room with monkeys previously infected by intravenous or subcutaneous injection of tubercle bacilli. After 391 days of this form of exposure, one of these animals died with tuberculosis. At 648 days, a second monkey died without gross evidence of tuberculosis. The 2 other animals remain healthy and tuberculin negative after 21 months of exposure to the various tuberculous monkeys of the isolation room.

In the monkey which died after 391 days, the anastomosis was found to be patent. Extensive conglomerate areas of caseation were present in the right lung, the side of the systemic pulmonary anastomosis. The striking difference

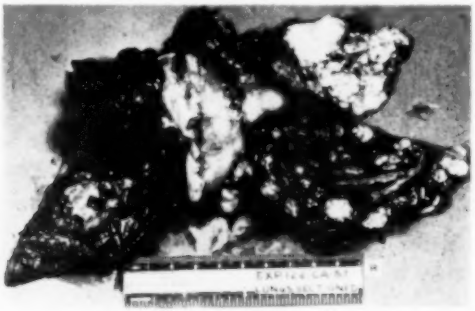

FIG. 5. (Monkey CA 57). Anastomosis between innominate and right pulmonary artery in monkey exposed to infected monkeys in "natural infection" experiment. Dorsal view of sectioned lung, showing extensive conglomerate caseous lesions in right lung.

in the extent of the tuberculous process in the two lungs in this monkey may be seen in figure 5.

Extrapulmonary lesions in this "naturally infected" monkey were similar in character and distribution to those encountered in the intravenously infected monkeys. The lesions were most prominent in the liver and spleen. Microscopic studies confirmed the gross findings.

Anastomosis Between a Systemic Artery and the Descending Trunk of the Pulmonary Artery in Monkeys Infected Intravenously After Operation

In 6 monkeys an end-to-end anastomosis was carried out between the innominate or left subclavian artery and the descending trunk of the corresponding pulmonary artery (figures 1 B and C). In 3 of these animals the branches of the pulmonary artery to the upper lobe of the lung were ligated (I 77, I 85, and I 86); in the 3 other monkeys the upper lobe branches of the pulmonary artery were left undisturbed (I 73, I 74, and I 75). The monkeys were infected with the

standard dose (10^{-4} mg.) of tubercle bacilli by intravenous injection 21 to 49 days after operation. These animals lived from 70 to 280 days after inoculation. Pertinent data for these animals are summarized in table 1. The anastomosis was found to be patent at autopsy in each of the 6 monkeys.

One animal (I 86), which was sacrificed 301 days after operation, showed no evidence of tuberculosis at autopsy. In the other 5 monkeys the extent of the pulmonary disease as seen at autopsy was greater in the lung on the side of the arterial alterations. Large conglomerate caseous lesions were present in the middle and lower lobes supplied by the arterial anastomosis in each instance (figure 6); while the upper lobe and the contralateral lung in 3 of the 5 monkeys showed smaller, scattered tubercles, usually of the miliary type. In one animal (I 85) in which the upper lobe branches of the right pulmonary artery were ligated at the time of anastomosis between the innominate artery and the descending

FIG. 6. (Monkey I 77). Anastomosis between innominate and descending trunk of right pulmonary artery in monkey infected by intravenous injection of 10^{-4} mg. of tubercle bacilli after operation. Dorsal view of sectioned lungs, showing extensive caseous lesions in middle and lower lobes of right lung.

trunk of the right pulmonary artery, there were extensive caseous changes in all lobes of the right lung. In contrast, the left lung showed scattered miliary tubercles. In another animal (I 74) in which the upper lobe branches were left intact at the time of the anastomosis, the upper as well as the middle and lower lobes were involved in the caseous process.

Extrapulmonary lesions in these animals were present in liver, spleen, and lymph nodes. Microscopic study of sections from the lungs and other viscera confirmed the gross findings.

Systemic Pulmonary Anastomosis in Monkeys Infected Intravenously with a Large Dose of Bacilli Before Operation

Four monkeys were given a one-milligram dose of tubercle bacilli by intravenous injection. The day after injection the animals were submitted to operation. Anastomosis between the end of a systemic artery and the end of the

corresponding pulmonary artery was carried out in 2 of the monkeys; in the other 2 animals, end-to-end anastomosis was done between the left subclavian artery and the descending trunk of the left pulmonary artery. In another monkey (No. 106), end-to-end anastomosis between the left subclavian artery and the left pulmonary artery was done and 1 mg. of tubercle bacilli was injected directly into the pulmonary arterial circulation at operation. One-half of the dose was injected into the right pulmonary artery and the remaining half into the left pulmonary artery.

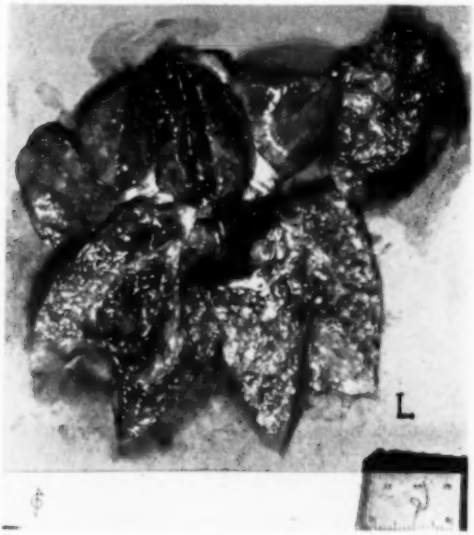

FIG. 7. (Monkey C 24). Anastomosis between left subclavian and descending trunk of left pulmonary artery in monkey infected by intravenous injection of 1 mg. of tubercle bacilli before operation. Death 27 days later. Ventral view of sectioned lung, showing caseous lesions concentrated in middle and lower lobes of left lung.

The 5 monkeys which received the large dose of tubercle bacilli lived for only 17 to 27 days after inoculation. The pertinent data for these monkeys are summarized in table 1. The anastomosis was patent at autopsy in each instance.

In 2 of the 3 monkeys (Nos. 106 and 23) with an anastomosis between the end of a systemic artery and the end of the ipsilateral pulmonary artery, the extent of the pulmonary disease as seen at autopsy was greater in the lung on the side of the anastomosis. The lesions were larger and more caseous in this lung. The third animal (C 18) showed diffuse miliary tuberculosis which involved both lungs equally.

One of the 2 monkeys with end-to-end anastomosis between the left subclavian artery and the descending trunk of the left pulmonary artery

showed at autopsy extensive caseous consolidation of the left middle and lower lobes, while miliary lesions were present in the other lung and in the left upper lobe (C 24). These findings are illustrated in figure 7. The other monkey showed diffuse miliary tubercles which were equally distributed throughout both lungs (C 17).

Extrapulmonary lesions in this group of animals were similar in character and distribution to those encountered in the monkeys which received the smaller,

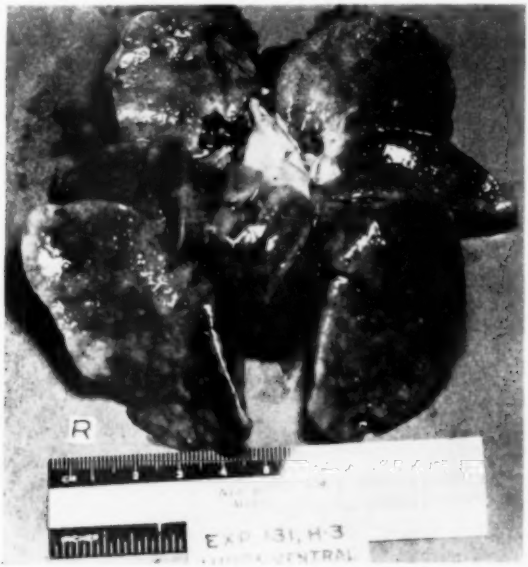

FIG. 8. (Monkey H 3). Control thoracotomy, right, in monkey infected by subcutaneous injection of 10^{-4} mg. of tubercle bacilli after operation. Ventral view of lungs, showing symmetrically distributed miliary tubercles.

"standard" dose (10^{-4} mg.) of bacilli. Microscopic studies confirmed the gross findings.

Control Thoracotomy

In 8 monkeys thoracotomy was carried out but no anastomosis was done. Four of these animals (I 76, H 6, H 42, and H 43) were infected with the standard dose (10^{-4} mg.) of tubercle bacilli by intravenous injection 6 to 21 days after operation. Two other monkeys (H 3 and H 10) received the standard dose of bacilli by subcutaneous injection 5 to 20 days after operation. The two remaining animals (CA 70 and CA 44) were confined to individual cages in the same isolation room with the infected monkeys as "natural infection" controls. The in-

jected animals lived 91 to 352 days. The two control animals in the "natural infection" experiment died 221 and 622 days, respectively, after the conditions of natural exposure were initiated. Pertinent data for these animals are summarized in table 1.

At autopsy in 7 of these 8 monkeys, the lungs showed an equal distribution of tubercles of miliary type, ranging from 1 to 5 mm. in diameter. There were no observable differences between the lung on the side of thoracotomy and the opposite lung from the standpoint of character or extent of the disease process. Typical findings at autopsy in the lungs of these animals are illustrated in figure 8. One of the control animals in the "natural infection" group died after 622 days of exposure, with no evidence of tuberculosis at autopsy.

Extrapulmonary lesions in these control animals were similar in character and distribution to those in the monkeys with systemic pulmonary shunts. Microscopic study of sections from the lesions confirmed the gross findings.

DISCUSSION

The results of these experiments indicate that, in monkeys with tuberculosis induced by various methods of exposure, diversion of systemic blood into a pulmonary artery produces a pathologic process which differs from the disease in control animals. When this diversion is accomplished by an end-to-end anastomosis between a systemic artery and a pulmonary artery, the lung on the side of operation usually shows massive conglomerate lesions with extensive caseation. In contrast, the opposite lung generally shows the miliary form of tuberculosis typically found in both lungs of control animals. When an end-to-end anastomosis is made between a systemic artery and the descending trunk of a pulmonary artery, massive caseous lesions develop in the middle and lower lobes of the lung on the side of the anastomosis; the remaining lobes usually show miliary tubercles similar to the lesions in the lungs of control animals. However, when an anastomosis between a systemic artery and the descending trunk of the pulmonary artery is combined with ligation of the branches of the pulmonary artery to the upper lobe, extensive caseous changes may develop in the entire lung on the side of operation.

These experiments confirm and extend the previous observations of the effects of systemic pulmonary anastomosis in monkeys infected with a standard dose (10^{-4} mg.) of tubercle bacilli by intravenous injection before operation (1). In the previous studies this preoperative injection was designed to effect equal seeding of the two lungs with the initial dose of organisms. In the present investigation emphasis was placed on exposure of the animals to tubercle bacilli *after* the end-to-end systemic pulmonary anastomosis had been performed. Under the anatomic conditions obtaining after an anastomosis of the type used in these experiments, it is apparent that bacilli injected into the saphenous vein *after* operation are directed primarily to the lung contralateral to the end-to-end systemic pulmonary anastomosis. Despite the probable heavier initial seeding of this contralateral lung with bacilli, the disease process in these animals at autopsy was usually found to be more extensive in the lung on the side of the anastomosis.

The experiments involving a large dose (1 mg.) of tubercle bacilli demonstrate that in so short a period as 3 to 4 weeks, severe caseous changes can become manifest in the pulmonary tissue supplied by the systemic pulmonary anastomosis. The most striking examples of extensive caseation, however, have been encountered in the lungs of the monkeys which received a smaller dose of organisms; this permitted their disease to develop for a much longer period of time.

We have previously pointed out that the same extensive caseous changes develop in the lungs of monkeys with induced tuberculosis which undergo such widely different operative procedures as ligation of a pulmonary artery and anastomosis between a systemic and pulmonary artery. A lung with a ligated pulmonary artery is supplied only by the bronchial artery. In contrast, a lung with a systemic pulmonary anastomosis is supplied not only by the bronchial artery but by the systemic arterial blood flowing through the anastomosis. The blood flow under the latter conditions obviously exceeds that through the bronchial arteries alone. In both cases, however, the lung on the side of operation is perfused only by fully oxygenated blood in contrast to a normal lung which receives a mixture of fully oxygenated and partly oxygenated blood.

As a result of this investigation and of our previous studies, it may be concluded that "arterialization" of a lung or a segment of the lung in monkeys with tuberculosis induced by various modes of exposure results in extensive caseous changes in the arterialized pulmonary tissue. It is our present opinion that these experiments involving ligation of pulmonary arteries and systemic pulmonary anastomosis indicate that the fundamental hemodynamic factor responsible for the extensive caseous changes in the tuberculous process is neither increased blood flow, increased blood pressure, nor unequal recirculation of tubercle bacilli. These experiments suggest that the caseous changes which are encountered are related to high oxygen tension in the blood perfusing the arterialized pulmonary tissue.

The growth of tubercle bacilli *in vitro* has been shown to be enhanced by high concentrations of oxygen (5, 6). Rich and Follis (7) have shown that the development of experimental tuberculosis in guinea pigs may be strikingly inhibited by reducing the environmental oxygen to a concentration of 9 to 10 volumes per cent. The present findings seem to be in general agreement with these observations and indicate that an increase in the concentration of oxygen available to tubercle bacilli growing *in vivo* results in a severe extension of the tuberculous process.

Experiments are in progress to assess the effects of elevated environmental oxygen levels on pulmonary tuberculosis in animals. Further study is being made of the effects of systemic pulmonary anastomosis and ligation of pulmonary arteries in monkeys which develop tuberculosis by the airborne or "natural infection" route.

SUMMARY

In the course of a continuing investigation of the effect of alterations in the pulmonary arterial circulation on tuberculosis in monkeys, 31 additional monkeys have been studied. All of these animals were subjected to thoracotomy. In 8

monkeys this constituted the only operative procedure; in the remaining 23, various alterations of the pulmonary circulation were produced. The monkeys were exposed to various modes and degrees of infection with virulent human tubercle bacilli both before and after surgery. These variations in conditions of exposure were designed to elucidate previous observations which showed a greater severity of the tuberculous process in the lung or lobe at the site of an arterial ligation or a systemic-pulmonary arterial anastomosis.

Results in the present investigation indicate that the tuberculous process is more severe on the side of a systemic-pulmonary anastomosis with both large and small dosages of organisms, with postoperative as well as preoperative inoculations, and with infection by both intravenous and subcutaneous routes. Incomplete data on infection by the airborne ("natural infection") route suggest that the same results are obtained with this mode of infection. In those animals subjected to thoracotomy only, there was no demonstrable difference in the tuberculous process in the two lungs, regardless of the mode of infection.

When ligation or anastomosis is confined to a portion of one lung, the tuberculous process is found to be more severe in that portion of the lung, in contrast to the findings in the remainder of the same lung and in the opposite lung where a miliary type of disease typical of unoperated control animals is observed.

These observations tend to substantiate our previous impression that induced pulmonary tuberculosis in monkeys is unfavorably affected in any segment of the lung perfused by fully oxygenated blood.

SUMARIO

Tuberculosis Experimental: III. Nuevas Observaciones Relativas a los Efectos de la Alteración de la Circulación Arterial Pulmonar sobre la Tuberculosis de los Monos

En el transcurso de una investigación continua del efecto de las alteraciones de la circulación arterio-pulmonar sobre la tuberculosis del mono, 31 monos más han sido estudiados. Todos esos animales fueron sometidos a la toracotomía. En 8, ésta constituyó el único procedimiento operatorio; en los otros 23, se produjeron varias alteraciones de la circulación pulmonar. Tanto antes cuanto después de la cirugía, los monos fueron expuesto a distintas formas y grados de infección con bacilos tuberculosos humanos virulentos. Esas variaciones en las condiciones de la exposición tenían por fin dilucidar previas observaciones de los AA., que mostraban mayor intensidad del proceso tuberculosos en el pulmón o lóbulo del sitio de una ligadura arterial o de una arterioanastomosis somático-pulmonar.

Los resultados de la investigación actual indican que el proceso tuberculoso es más grave del lado de una anastomosis somático-pulmonar tanto con grandes como con pequeñas dosis de microbios, con inoculaciones post- así como preoperatorias y con infección transmitida por las vías tanto endovenosa cuanto subcutánea. Datos incompletos acerca de la infección porvía aérea ("infección natural") sugieren que lo mismo reza con esa forma de infección. En los animales sometidos únicamente a la toracotomía, no hubo diferencia observable en el proceso tuberculosos en los dos pulmones, independientemente del modo de infección.

Cuando se limita la ligadura o la anastomosis a una porción del pulmón, el proceso tuberculosos resulta ser más grave en dicha porción, en contraposición a los hallazgos en el resto del mismo pulmón y en el pulmón opuesto en los que se observa una forma granúlica de la enfermedad, típica de los animales testigos no operados.

Estas observaciones tienden a apoyar la previa impresión de los AA., de que la tuberculosis pulmonar inducida en los monos es afectada desfavorablemente en cualquier segmento del pulmón perfundido por sangre plenamente oxigenada.

RESUME

Tuberculose expérimentale: III. Nouvelles observations sur les effets de l'altération de la circulation artérielle pulmonaire dans la tuberculose du singe

Au cours d'une enquête continue sur l'action des modifications de la circulation artérielle pulmonaire dans la tuberculose chez le singe, un groupe supplémentaire de 31 singes a été étudié. Chaque animal a été soumis à la thoracotomie. Chez 8 singes cette intervention a été le seul procédé chirurgical utilisé; chez les autres singes, diverses modifications de la circulation pulmonaire ont été effectuées. Les singes ont été soumis à divers modes et degrés d'infection, à l'aide de bacilles humains virulents, à la fois avant et après l'intervention chirurgicale. Ces variations, dans les conditions de l'exposition à l'infection, ont été faites dans le but de vérifier nos observations précédentes, qui montraient que le processus tuberculeux était plus marqué dans le poumon, ou dans le lobe, au niveau d'une ligature d'artère ou d'une anastomose entre le système artérial du poumon et la circulation générale.

Les résultats de l'enquête actuelle, indiquent que le processus tuberculeux est plus sévère du côté de l'anastomose circulation artérielle du poumon-circulation générale, que les doses d'inoculation soient fortes ou faibles, que les inoculations soient pré ou post-opératoires et que l'inoculation soit faite par voie sous-cutanée ou intraveineuse. Des données incomplètes sur l'infection spontanée suggèrent que les mêmes résultats sont obtenus par ce mode d'infection. Chez les animaux soumis à la thoracotomie, aucune différence appréciable dans le processus tuberculeux n'a été observée, quel qu'ait été le mode d'infection.

Quand la ligature ou l'anastomose est limitée à un segment de l'un des poumons, on constate que le processus tuberculeux est plus sévère dans ce segment pulmonaire par comparaison avec les constations faites dans l'autre partie du même poumon et dans le poumon opposé, où on observe un type miliaire caractéristique de l'affection chez les animaux-témoins non opérés.

Ces observations tendent à confirmar notre impression antérieure que, chez le singe, la tuberculose pulmonaire par inoculation est défavorablement influencée dans tout segment pulmonaire soumis à une perfusion de sang dont la teneur en oxygène est complète.

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IN VIVO OBSERVATIONS ON THE EFFECT OF CORTISONE ON EXPERIMENTAL TUBERCULOSIS, USING THE RABBIT EAR CHAMBER TECHNIQUE[1,2,3]

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(Received for publication May 16, 1951)

INTRODUCTION

Since adrenocorticotropic hormone (ACTH) and cortisone have a profound effect on a variety of inflammatory reactions, both infectious and noninfectious (1, 2), it was to be expected that the course of tuberculous infection would be modified by these compounds. In an effort to elucidate the nature of this change in tissue reaction, an *in vivo* study was undertaken of the effects of cortisone on tuberculous infection using the rabbit ear chamber technique.

The rabbit ear chamber provides a thin layer of living vascularized tissue 40 to 50 microns thick which can be inoculated directly with living virulent tubercle bacilli. The course of infection can be observed in the living animal over a period of weeks and months, and serial microscopic observations can be made on the same tubercle. The method has the disadvantage of being laborious so that large numbers of animals cannot be studied. It has the advantage, however, of showing the dynamics of change in the same tuberculous lesion before, during, and after treatment with cortisone.

In the unsensitized animal the initial response to the presence of living virulent tubercle bacilli is minimal. With the development of hypersensitivity, however, there is progressive vascular damage characterized by dilatation of blood vessels, sticking of leukocytes to vascular endothelium, and diapedesis of white blood cells. This vascular damage is followed by hemoconcentration, stasis, and thrombosis of small blood vessels with infarction of tissue and caseation (3).

METHODS AND MATERIALS

The rabbit ear chamber and the method of examination have been adequately described elsewhere (3, 4, 5). Observations are made on mature connective tissue supporting well-differentiated blood vessels which have grown onto a central table 8 mm. in diameter and 40 to 50 microns thick. A central plug can be withdrawn and the tissue directly inoculated with tubercle bacilli.

Photomicrographs made with a Leica micro-attachment and Kodachrome motion pictures made with an Eastman Kodak Special were taken at intervals during each experiment and facilitated evaluation of the reactions. The source

[1] From the Department of Medicine, University of Chicago, Chicago, Illinois.

[2] This investigation was supported by a research grant from the National Institutes of Health, Public Health Service.

[3] Presented before the Medical Session, as part of the symposium on *Laboratory and Other Basic Research* at the 47th annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, on May 16, 1951.

of illumination was a Bausch and Lomb spherical lamp, and a water filter was used to avoid heating the tissues.

Seven animals were used in these experiments. One animal had a chamber in each ear and so a total of eight chambers were inoculated with tubercle bacilli. Each animal was sensitized with BCG prior to inoculation of the chamber. A total of 16 mg. of BCG was given in divided doses in four subcutaneous sites on the abdomen one and one-half to three months prior to inoculation. All animals were cutaneous reactors to tuberculin at the start of the experiments.

TABLE 1

SCHEDULE OF TREATMENT IN ANIMALS GIVEN CORTISONE AFTER INFECTION WAS WELL ESTABLISHED

EXPERIMENT	NUMBER OF COURSES OF CORTISONE	LENGTH OF TREATMENT IN DAYS	DAILY DOSAGE
			mg.
1	1	5	10
2	2	5 (first course)	25
		4 (second course)	25
3	1	7	25
4	2	23 (first course)	10
		7 (second course)	10
5	1	19	10

TABLE 2

SCHEDULE OF TREATMENT IN ANIMALS GIVEN CORTISONE PRIOR TO INOCULATION AND FROM THE TIME OF INOCULATION

EXPERIMENT	DAYS OF TREATMENT BEFORE INOCULATION	DAYS OF TREATMENT AFTER INOCULATION	DAILY DOSAGE
			mg.
6	0	13	25
7	8	21	5
8	8	21	5

Each chamber was inoculated with approximately 0.001 to 0.002 mg. (wet weight) of Ravenel Rv freshly ground and suspended in saline. Tubercle bacilli were grown on Proskauer and Beck media.

The effects of cortisone on well-established tuberculous infection were studied in five chambers (table 1). Three animals received treatment from the day of inoculation and 2 of these animals were treated for eight days prior to inoculation as well (table 2). The dosage schedule and the length of treatment is given in tables 1 and 2. In two experiments (Experiments 2 and 4) the effect of two courses of treatment was studied. Experiments 5 and 6 were done on the same animal. The right ear was inoculated first (Experiment 6) and the effects of cortisone on the course of infection from the time of inoculation were studied. Subsequently the opposite ear was inoculated (Experiment 5) and the infection

was allowed to run its natural course until the thirty-sixth day when treatment was given. One animal (Experiment 4) received 100 mg. of streptomycin daily concomitant with cortisone therapy.

RESULTS

In all but one experiment, cortisone produced a significant reduction in the inflammatory reaction caused by living virulent tubercle bacilli in the hypersensitive rabbit. The results were similar in animals pretreated with cortisone, treated from the time of inoculation, and treated after infection was well established. The reduction in the inflammatory response was quantitative and was never complete. Three to six days of treatment with cortisone were necessary

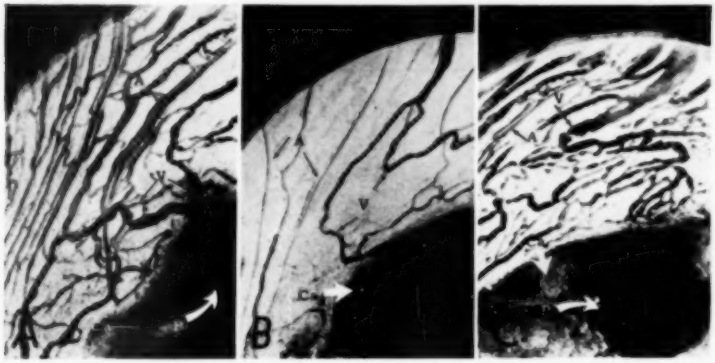

FIG. 1. A. Portion of a tubercle thirteen days after inoculation in an untreated animal. There is a caseous area (Ca) in lower left hand corner of photograph adjacent to the removable plug (P). Note dilatation of arterioles (A) and venules (V). (35×)

B. The same area after seven days of cortisone treatment (25 mg. daily). Note the increase in tone of both arterioles (A) and venules (V). (35×)

C. The same region thirty-three days after inoculation and 14 days after cessation of cortisone therapy. Blood vessels have dilated again. (35×)

before the full suppressive effect on the inflammatory reaction was observed. The effect of cortisone was reversible and, 2 to 4 days after treatment had been stopped, there was an exacerbation of the inflammatory reaction.

The results can best be analyzed in terms of the usual pathologic changes observed *in vivo* by the rabbit ear chamber technique.

Vascular tone: Generalized dilatation of all blood vessels in the chamber occurs in the untreated hypersensitive animal in response to tuberculous infection. Cortisone tends to reverse this usual reaction to infection, and more normal tone is maintained during treatment. In the animals pretreated with cortisone, there was even some increase in the vascular tone before the chamber had been inoculated.

Figures 1 and 2 illustrate the improvement in vascular tone during treatment of an established infection, and figures 3 and 4 show how tone tends to be maintained in an animal treated from the time of inoculation. This is a quantitive effect, however, and in figure 4C it will be seen that abnormal dilatation and constriction of an arteriole developed after twenty-one days of treatment. Much more marked dilatation occurred after treatment was stopped (figure 4D).

Damage to vascular endothelium: A characteristic pattern of endothelial damage has been found to occur in tuberculous infection as observed *in vivo* (3). This pattern begins with sticking of leukocytes to vascular endothelium and is followed by hemoconcentration, stasis, and finally thrombosis of vessels. Following the development of caseation, the most intense reaction occurs along the

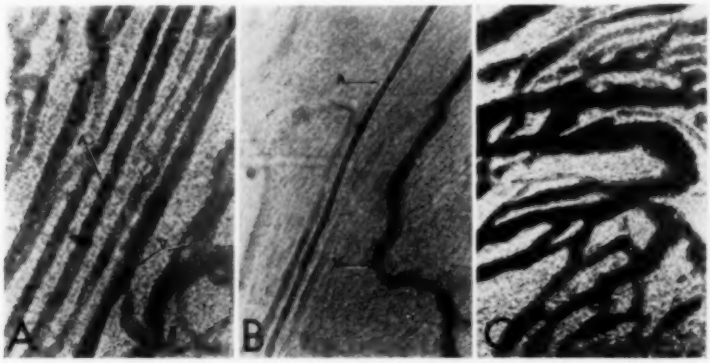

FIG. 2. A. Higher power of area shown in figure 1A thirteen days after inoculation. Not dilatation of arteriole (A) and venule (V) before cortisone. The hazy background is exudate. (100×)

B. The same area after seven days of cortisone therapy. (Higher power of region shown in figure 1B). There has been increase in vascular tone and decrease in exudate. (100×)

C. Higher power of area shown in figure 1C. Note marked dilatation fourteen days after stopping cortisone. (100×)

abscess edge and the caseous area extends by continued thrombosis of small blood vessels and infarction of adjacent tissue. There is usually evidence of diffuse endothelial damage, however, even some distance from the caseous area. Normal vascular endothelium has a characteristic refractile appearance and, when damaged, this refractile appearance tends to be lost.

Cortisone causes a quantitative reduction in the degree of vascular damage produced by tuberculous infection. In animals pretreated with cortisone and treated from the time of inoculation, a reduction in the usual explosive reaction is seen following the inoculation of tubercle bacilli in the untreated hypersensitive animal (figures 3 and 4). Sticking of leukocytes to vascular endothelium, stasis, and thrombosis do occur, but the reaction appears to be more localized.

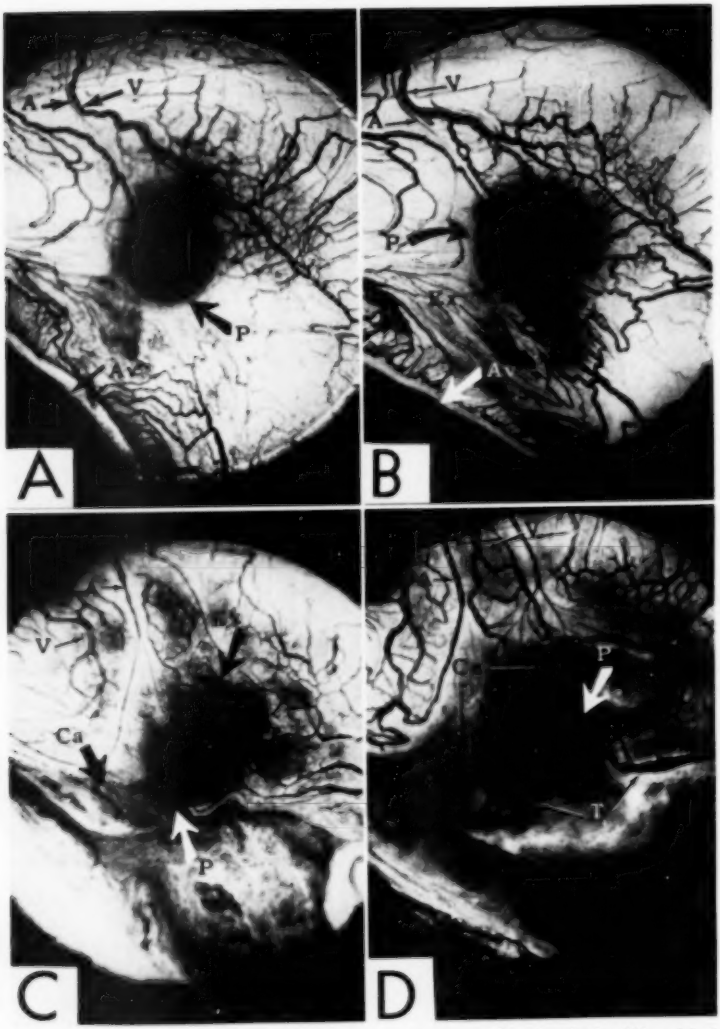

FIG. 3 A. Appearance of chamber prior to inoculation with tubercle bacilli and before treatment with cortisone. There is an avascular area (Av) at lower edge of table. The opaque area in the center is the end of the removable silver plug (P). (18×)

B. The same chamber five days after inoculation with tubercle bacilli and after thirteen days of cortisone therapy (5 mg. daily). Vascular tone is well maintained and only a small amount of exudate (Ex) has formed. Compare arteriole (A) and venule (V) in figures 3 A and 3 B. (18×)

C. The same tubercle twenty-one days after inoculation (twenty-nine days of cortisone). A caseous area (Ca) has developed and exudate (Ex) is more prominent, but tone is still well maintained. (18×)

D. The same tubercle twenty-eight days after inoculation and seven days after stopping cortisone. There has been extension of the caseous area (Ca) and fresh thrombi (T) are visible. Note the vascular dilatation (A and V). (18×)

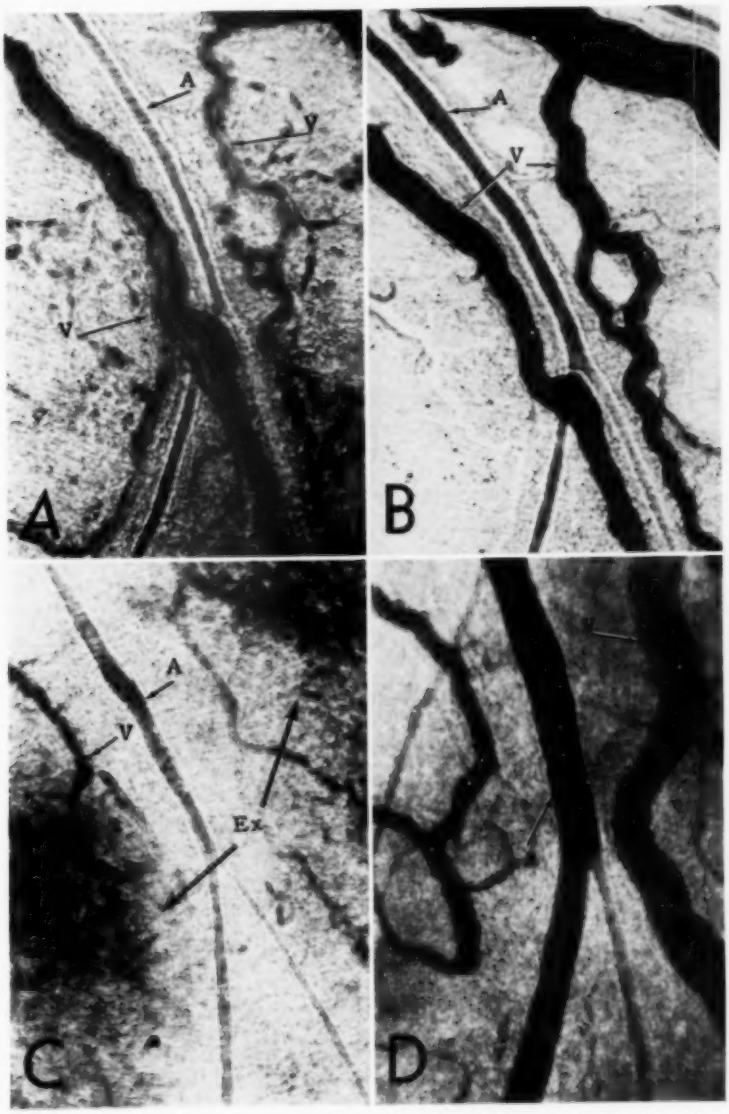

FIG. 4. A–D show higher power views of one area of the tubercle shown in figure 3.

A. Arteriole (A) and venules (V) shown in figure 3A. Before inoculation of chamber. (100×)

B. The same area five days after inoculation (thirteen days of cortisone). Note how well the vascular tone is maintained. There is no exudate. (100×)

C. The same area twenty-one days after inoculation (twenty-nine days of cortisone). There are localized areas of exudate (Ex). Vascular tone is maintained but the arteriole (A) shows abnormal dilatations and constrictions. (100×)

D. The same area twenty-eight days after inoculation and seven days after stopping cortisone. Note the dilatation of the arteriole (A) and venule (V). There is a generalized exudate (Ex) which obscures vessels. (100×)

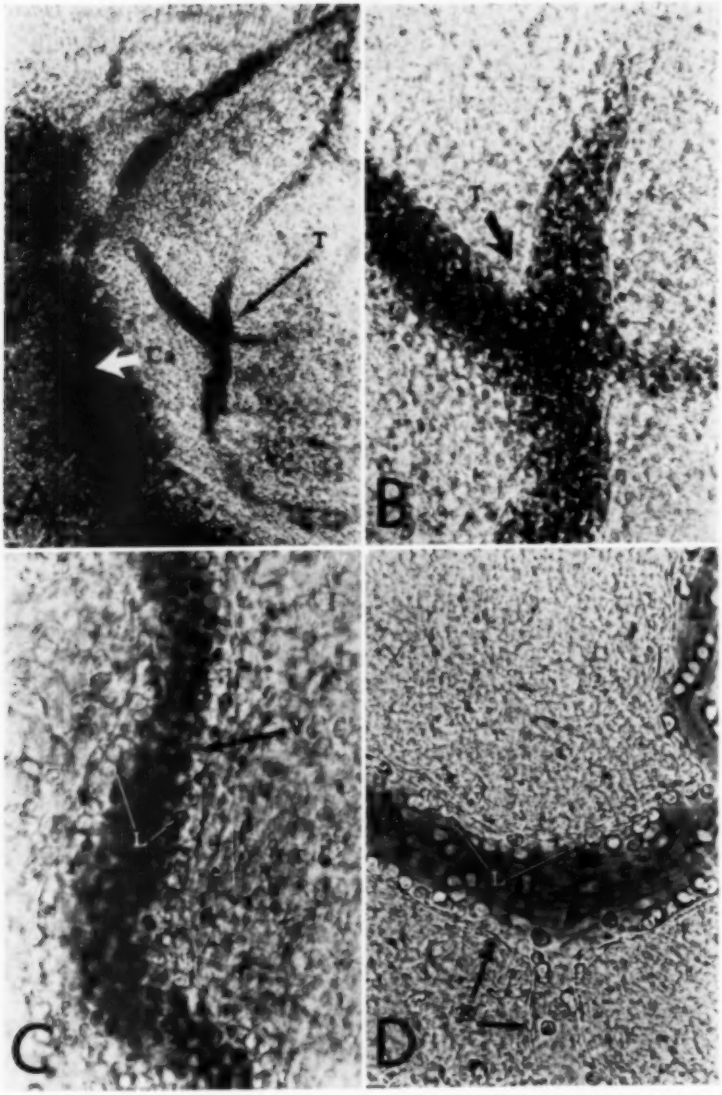

FIG. 5 A. A thrombosed (T) vessel adjacent to a caseous area (Ca) in an animal forty-seven days after inoculation and after twelve days of cortisone therapy. (100×)

B. Higher power view of thrombosed vessel (T) shown in figure 5A. (400×)

C. A venule some distance from caseous area in a tubercle thirty-five days after inoculation (before cortisone treatment). Note sticking of leukocytes (L). Endothelium is indistinct. (400×)

D. A venule in the same area after twelve days of cortisone. There is still sticking of leukocytes but note how distinctly endothelium (E) can be seen. (400×)

There is infarction of tissue and caseation, but vascular endothelium a short distance from the caseous area tends to maintain its normal refractile appearance.

Similarly, there is a reduction in the diffuse endothelial damage in animals treated after infection is well established. Thrombosis of blood vessels continues to occur along the caseous edge, however (figures 5A, 5B), and the caseous area enlarges during treatment (figure 3). Figures 5C and 5D demonstrate well the return toward normal of vascular endothelium in an animal treated after infection is well established.

Exudate: The exudate which forms in tuberculous infection as observed *in vivo* is derived largely from cells which have migrated through damaged vascular endothelium. In the untreated hypersensitive animal a generalized exudate covering the entire observation table develops during the first forty-eight hours after inoculation. In the animals pretreated and treated from the time of infection, there is a considerable reduction in the amount of exudate which presumably reflects the reduction in vascular damage. Exudate forms but, as may be seen in figures 3B, 3C, and 4C, tends to be more localized and develops more gradually. Several days after cessation of cortisone therapy, the exudate becomes generalized (figure 4D).

In animals treated after infection is established, exudate stops forming at the same rate, and after one to two weeks there is considerable clearing of exudate (figures 2A and 2B). Accumulation of macrophages continues to occur along the caseous edge, however, although never to the same degree as in the untreated animal.

Caseation: Following the infarction of tissue in tuberculous infection there is necrosis of the vascular area, and the region often becomes partially fluid. As noted previously, caseation occurs in animals treated with cortisone (figures 3A–3D) and therapy has no discernible effect on the fluidity of the caseous area.

Healing: Little data is available on healing from these *in vivo* studies on tuberculous infection. There was evidence of healing in only one experiment (Experiment 4), and this animal had received streptomycin prior to cortisone therapy. Streptomycin, 100 mg. daily, was continued during and after treatment with cortisone. During the twenty-three days of combined streptomycin and cortisone treatment there was some healing, but it was minimal. During the first seven days after cortisone therapy was stopped the healing which occurred was equal to that which had occurred during the previous twenty-three days; and twenty-eight days after cortisone had been stopped, the observation area had almost completely revascularized. (Two-thirds of the chamber had been caseous at the end of cortisone therapy.) Cortisone treatment for seven days given at the time the observation table was almost revascularized did not cause cessation of healing.

During the period of cortisone therapy the blood vessels appeared much more normal than they did during the period of rapid healing after cortisone was stopped.

Effect of dosage: In general, doses of 5 to 10 mg. of cortisone had a less pro found effect than 25 mg. daily. This was particularly apparent when given for

short periods of time. The one animal which showed no appreciable response to therapy was treated with 10 mg. daily for five days.

DISCUSSION

Cortisone therapy causes three consistent changes in the inflammatory reaction produced by tuberculous infection in the hypersensitive animal. First, vascular tone is better maintained. Second, there is a reduction in damage to arteriolar and venule endothelium, and vascular endothelium in the treated animal tends to maintain its normal refractile appearance. Third, as a result of the increased integrity of vascular endothelium, there is a decrease in diapedesis of leukocytes and a reduction in exudate. It is of interest to speculate on the cause of the reduction in inflammatory response produced by cortisone. There is little doubt that it is associated with a reduction in the reaction to tuberculoprotein. Various investigators (2, 6, 7) have reported partial suppression of the tuberculin reaction in man and animal following treatment with ACTH and cortisone. *In vivo* studies in this laboratory on the focal reaction have demonstrated a consistent depression of the response during cortisone therapy (8). These results, however, do not indicate whether the reduction in tuberculin hypersensitivity is a specific or nonspecific effect.

There is no general agreement at present on the role of ACTH and cortisone in altering antibody formation (1, 2), and no positive evidence exists that antibody production is suppressed in tuberculous infection. Similarly, cortisone does not appear to inhibit antibody-antigen union, at least *in vitro* (9).

An imposing body of evidence shows, however, that cortisone and ACTH can suppress inflammatory reactions to a wide variety of different stimuli (1, 2), including acute infections, wound healing, the Schwartzman phenomenon, chemical irritation, and thermal burns (10). This evidence suggests that the suppressive effects of cortisone on tuberculous infection are nonspecific; other studies with the rabbit ear chamber support this theory. An increase in vascular tone has been repeatedly observed in apparently normal chambers following three to four days of cortisone therapy, and nonspecific inflammatory changes have been shown to disappear during the same period of treatment (8). Cortisone suppresses the *in vivo* manifestation of serum sickness as observed in the ear chamber (11), and the manner in which it does so is entirely similar to the suppression of inflammation in tuberculous infection.

Since cortisone tends to reduce the reactivity of small blood vessels, it becomes apparent that disease states will be favorably or unfavorably effected according to the "usefulness" of the inflammatory response to the host. In wound healing and acute infections, the inflammatory reaction is "useful" to the host and, as might be expected, the effects of cortisone are unfavorable. In rheumatic fever, rheumatoid arthritis, and certain allergic states, the inflammatory reaction appears to have no value to the host and the effect of cortisone is beneficial.

Tuberculosis poses a more complex problem. On theoretical grounds one might expect a reduction of tissue destruction together with poorer localization of tubercle bacilli. It is obvious from these and other experiments (12), however, that

caseation is not suppressed. It is possible that the reduction in exudate results in greater multiplication of infecting organisms so that, even though the ability of the tissue to react is quantitatively reduced, the stimulus for reaction is greater. This reaction would also explain the apparent flare-up of infection after therapy is stopped.

Probably no absolute answer to the "harmfulness" or "usefulness" of cortisone on tuberculous infection is possible. The results seem to be variable according to the number and virulence of the infecting organisms, the degree of hypersensitivity and immunity the dosage of cortisone, and the organ involved. In general, however, a drug which can profoundly reduce inflammation is a potential danger in any infection, particularly since the harmful effect may not be apparent until after cortisone therapy has been stopped.

SUMMARY

Using the rabbit ear chamber technique, an *in vivo* study has been made of the effects of cortisone on tuberculous infection.

Cortisone produces a quantitative reduction in the inflammatory response of the hypersensitive animal to tuberculous infection. Three consistent changes are produced in the inflammatory reaction which are common to other types of inflammation studied. First, vascular tone is better maintained. Second, there is a reduction in damage to arteriolar and venule endothelium. Third, as a result of the increased integrity of vascular endothelium, there is a decrease in diapedesis of leukocytes and a reduction in exudate.

Although cortisone delays tissue destruction, the reduction in inflammation causes poorer localization of infection.

SUMARIO

Observaciones in Vivo del Efecto de la Cortisona sobre la Tuberculosis Experimental, Usando la Técnica de la Cámara de la Oreja del Conejo

Usando la técnica de la cámara de la oreja del conejo, hízose un estudio *in vivo* de los efectos de la cortisona sobre la infección tuberculosa.

La cortisona produce una reducción cuantitativa en la respuesta inflamatoria del animal hipersensible a la infección tuberculosa. Nótanse tres alteraciones constantes de la reacción inflamatoria que comparten otras formas de inflamación estudiadas. Primera, se mantiene mejor la tonicidad vascular. Segunda, disminuyen las lesiones del endotelio arteriolar y venular. Tercera, a consecuencia de la mayor integridad del endotelio vasular, disminuye la diapédesis de los leucocitos e igualmente el exudado.

Aunque la cortisona demora la histólisis, la reducción de la inflamación afecta la localización de la infección.

RESUME

Observations faites in vivo sur l'action de la cortisone dans la tuberculose expérimentale en utilisant l'oreille moyenne du lapin

Une étude *in vivo* de l'action de la cortisone sur l'infection tuberculeuse a été effectuée en utilisant le pavillon de l'oreille du lapin (procédé "ear chamber").

La cortisone détermine une réduction quantitative de la réaction inflammatoire chez cet animal hypersensible à l'infection tuberculeuse. Trois modifications classiques et habi-

tuelles dans les autres types de réactions inflammatoires étudiées, se manifestent. Primo, le tonus vasculaire est mieux conservé. Deuxièmement, l'altération de l'endothélium des artérioles et des veinules est réduite. Troisièmement, en raison de l'amélioration des conditions d'intégrité de l'endothélium vasculaire, il y a une diminution de la diapédèse leucocytaire et une réduction de l'exudat.

Tandis que la cortisone retarde la destruction des tissus, la réduction du processus inflammatoire est un obstacle a la localisation de l'infection.

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COMPARISON OF GROWTH AND AUTOLYSIS OF TWO STRAINS OF TUBERCLE BACILLI[1,2]

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(Received for publication August 15, 1951)

INTRODUCTION

When tubercle bacilli were grown in a simple medium containing an excess of glucose but limiting amounts of a nitrogen source such as NH_4Cl, it was found that a decrease in optical density of the culture followed the initial period of growth (1). It was suggested that under these conditions the bacteria utilized their own nitrogenous resources for growth and that these were thereby depleted to a point where cellular disintegration (lysis) occurred. In the present study, analyses of nitrogen content were made and the results were found to support this hypothesis. The response to the addition of the missing nutrients after culture in incomplete media has also been studied. A comparison of two strains of *M. tuberculosis*, H37Rv and BCG, in this respect showed significant differences in subsequent growth rates.

EXPERIMENTAL METHODS

The H37Rv was the same culture as that used in the previous experiments (1). The BCG strain was obtained through the courtesy of Dr. K. Birkhaug. The bacteria were grown in two Roux bottles, each containing 200 ml. of a basal medium of the following composition: KH_2PO_4, 1 gm.; $Na_2HPO_4 \cdot 12H_2O$, 6.3 gm.; $MgSO_4 \cdot 7H_2O$, 0.02 gm.; $CaCl_2$, 0.0005 gm.; polyoxyethylene sorbitan monooleate (Tween 80), 0.2 ml.; bovine albumin (plasma fraction V, Armour Company), 1 gm.; H_2O, 1 liter.

The nutrients added to the basal medium were glucose to 1 per cent and NH_4Cl, 0.05 to 0.1 per cent, or sodium glutamate, 0.1 to 0.2 per cent.

After growing at 37° C. for four to six days, the cultures were centrifuged at 4° C. for thirty minutes at 2,400 g, and the bacteria were washed twice with the basal medium to remove residual nutrients. The washed bacteria from 400 ml. of culture were then suspended in 10 ml. of the basal medium. Three aliquots of this suspension were taken. To one, which was transferred to a weighed tube, formalin was added to a final concentration of 1 per cent. After twenty-four hours at 4° C., this suspension was washed three times with distilled water, dried at 100° C. to constant weight, and nitrogen determined on a weighed portion by the Kjeldahl method. Another aliquot of the 10 ml. suspension was transferred aseptically to a Roux bottle containing 200 ml. of the basal medium to which 1 per cent glucose but no nitrogen source was added. The third aliquot was inoculated into 200 ml. of the basal medium without any carbon or nitrogen source.

The cultures in the Roux bottles were incubated at 37° C. in a horizontal position and shaken twice daily. Optical density measurements were made on 6 ml. samples removed to 20- by 130-mm. screw-cap tubes, as previously described (1). When necessary, the samples were incubated further and added to the main culture when the bacteria were finally collected. The bacteria were collected for analysis after four to five days' incubation, when

[1] From the New York University College of Medicine, and Division of Tuberculosis, Public Health Service.

[2] This investigation was supported by a research grant from the National Institutes of Health, Public Health Service.

the optical density had reached a maximum, and after fifteen days when autolysis had been allowed to proceed for ten days. The data obtained are shown in table 1.

To analyze the response to nutrients after nitrogen and nitrogen and carbon starvation, suspensions of bacteria which had been grown in the basal medium with 0.05 per cent ammonium chloride and 1 per cent glucose were washed and introduced in equal amounts into flasks, one containing 200 ml. of the basal medium and the other containing the same amount of the basal medium plus 1 per cent glucose. The contents of each of the flasks were distributed to culture tubes in 6 ml. portions, incubated at 37°C. in a slanted position, and shaken twice daily. Immediately after inoculation and at various times up to twenty-three days later, 0.3 ml. of a concentrated solution of the missing nutrients was added to two tubes of each series to make the concentration of ammonium chloride 0.05 per cent and that of glucose 1.0 per cent. Optical density readings were taken daily with a Coleman spectrophotometer, and the values were converted to logarithms to the base 2. These $\log_2$ values were then plotted as a function of time to give the growth curves. From these curves, the time required to reach the exponential growth rate was obtained by inspection. The generation time, i.e., the average time for one cell division during exponential growth, was taken as the time required for the $\log_2$ of the optical density to increase by one log unit during the exponential phase. Examples of the types of curves obtained are shown in figures 1 and 2.

RESULTS

Nitrogen Content—H37Rv

The nitrogen content of the bacteria used as inoculum varied between 7 and 8 per cent by weight, being somewhat higher with sodium glutamate than with ammonium chloride as the nitrogen source.

After incubation for four to five days in the absence of an external source of nitrogen but with glucose present, the bacterial nitrogen recovered was 77 to 97 per cent of the amount originally present in the inoculum (table 1, column 8). After fifteen days the nitrogen recovered was reduced to 48 per cent of the amount originally present or, in other words, approximately 50 per cent of the bacterial nitrogen was lost to the medium in that time. The bacterial dry weight increased by a factor of approximately 2 in four to five days, but by the fifteenth day it was reduced to little more than the initial amount. In the four- to five-day period when bacterial weight doubled, the nitrogen content (as per cent of the bacterial dry weight) was reduced to approximately 40 per cent of that of the inoculum, and a similar value was obtained for the surviving bacteria at the end of fifteen days (table 1, column 7). In striking contrast to this situation, incubation in the absence of both nitrogen and carbon sources resulted in a loss of only 15 per cent of the bacterial nitrogen to the medium and a reduction in the nitrogen per unit dry weight of only 15 per cent. The results obtained during nitrogen and carbon starvation were not significantly affected by the presence or absence of serum albumin (compare 5b and 5c, table 1). It was found previously that,

with 0.1 per cent albumin as the only carbon source, no measurable growth was obtained (1).

TABLE 1

CHANGES OF DRY WEIGHT, NITROGEN CONTENT, AND DENSITY OF SUSPENSIONS OF TUBERCLE BACILLI AFTER EXPOSURE TO NITROGEN STARVATION WITH AND WITHOUT GLUCOSE

EXPERIMENT	CULTIVATION OF INOCULUM	NITROGEN STARVATION		WEIGHT IN MG. (W); N CONTENT, PER CENT (N); CULTURE DENSITY (D)			W, N, D	N RECOVERED* PER CENT
		Supplement to basal medium	Duration in days		Initial	Final	FINAL INITIAL	
1	glutamate 0.1 per cent; glucose 1 per cent	glucose 1 per cent	4	W	13.9	27.6	1.98	77
				N	7.5	2.96	0.40	
				D	0.183	0.475	2.60	
2	glutamate 0.1 per cent; glucose 1 per cent	glucose 1 per cent	5	W	25.5	54.9	2.12	78
				N	8.04	2.94	0.37	
				D	0.310	0.854	2.75	
3	glutamate 0.2 per cent; glucose 1 per cent	glucose 1 per cent	4	W	26.9	51.4	1.91	82
				N	7.95	3.40	0.43	
				D	0.328	0.839	2.56	
4	NH_4Cl 0.05 per cent; glucose 1 per cent	glucose 1 per cent	4	W	16.7	37.5	2.25	97
				N	7.05	3.04	0.43	
				D	0.187	0.569	3.04	
5a	NH_4Cl 0.05 per cent; glucose 1 per cent	glucose 1 per cent	15	W	14.7	17.25	1.17	48
				N	7.19	2.92	0.41	
				D	0.185	0.319	1.72	
5b	NH_4Cl 0.05 per cent; glucose 1 per cent		15	W	14.7	14.6	0.99	84
				N	7.19	6.09	0.85	
				D	0.185	0.182	0.98	
5c	NH_4Cl 0.05 per cent; glucose	(albumin absent also)	15	W	14.7	13.45	0.91	82
				N	7.19	6.19	0.86	
				D	0.185	0.177	0.96	

* Percentage of cellular nitrogen in the inoculum recovered in the bacteria following starvation.

Growth Response

Apparent lag: After incubation of BCG for as long as twenty days in the absence of both nitrogen and glucose sources, growth at an exponential rate began immediately after adding the missing nutrients. In the case of H37Rv, there was no significant lag until the fifteenth to twenty-third day of starvation. When the medium was deficient only in the nitrogen source, however, the time required to reach an exponential rate of growth rose to approximately 160 hours

at five to six days in both strains. After six days there was a decrease in this apparent lag followed by a subsequent increase. The increase in the lag time during the first six days is obviously related to the lysis which occurs in this time

TABLE 2

GENERATION TIME OF TUBERCLE BACILLI AND APPARENT LAG IN HOURS AFTER NITROGEN AND NITROGEN PLUS CARBON STARVATION

H37Rv

	DAYS OF STARVATION									
	0	1	2	4	6	8	11	15	18	23
Generation Time										
Nitrogen and carbon starvation										
a	38	35	33	36	56	52	55	47	56	50
b	36	36	35	39	48	43	45	53	56	58
Nitrogen starvation										
a	36	36	42	48	40	47	39	47	46	60
b	38	38	41	52	46	47	54	—	42	113
Time to Exponential Growth										
Nitrogen and carbon starvation										
a	0	0	34	0	51	0	0	120	123	146
b	0	24	0	0	0	0	0	0	0	145
Nitrogen starvation										
a	0	44	96	135	164	127	114	72	48	116
b	0	44	97	100	164	109	96	119	47	126

BCG

	DAYS OF STARVATION							
	0	2	3	5	9	12	15	20
Generation Time								
Nitrogen and carbon starvation								
a	52	54	53	57	70	80	113	118
b	54	48	52	52	74	63	97	118
Nitrogen starvation								
a	52	72	104	92	93	103	89	88
b	51	82	114	90	113	98	87	118
Time to Exponential Growth								
Nitrogen and carbon starvation								
a	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0
Nitrogen starvation								
a	0	39	123	161	116	120	149	155
b	0	0	97	131	68	92	139	107

(1). The cause of the subsequent decrease in lag time is not self evident but may possibly be attributed to utilization of the products of lysis by the surviving bacteria.

Generation time: With both nitrogen and carbon sources lacking, there was no

rise in the generation time of H37Rv or BCG during the first four to five days. Subsequently, there was a significant, but not progressive, rise in H37Rv, while in BCG there was a continuing increase in generation time beginning at the ninth day. With only glucose absent, H37Rv showed no change until the fourth to sixth day when there was a slight rise and again on the twenty-third day when there was a marked rise. Under the same conditions, BCG showed a pronounced

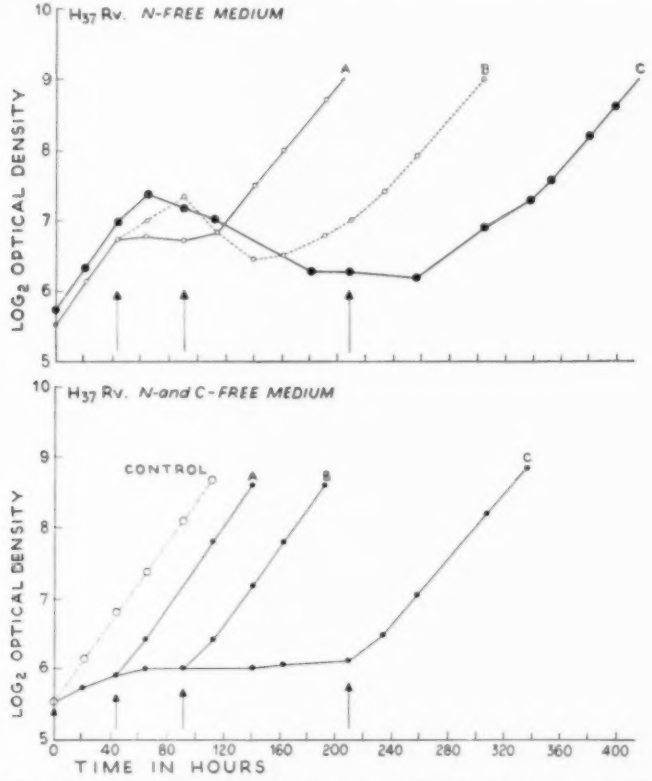

FIG. 1. Growth of H37Rv after nitrogen and nitrogen plus carbon starvation.

increase in generation time as early as the second or third day which persisted to the end of the experimental period.

DISCUSSION

From the data presented (figures 1 and 2, table 2) it is clear that, even when nitrogen is added to the nitrogen-deficient cultures before there is any obvious

reduction in growth rate as indicated by optical density, there is, nevertheless, an appreciable lag before the resumption of an exponential rate of growth. When the nitrogen addition is made at the point of incipient lysis (three to five days after the cultures were started), a period of decreasing optical density ensues before growth is again resumed. The first nitrogen addition was made at the end of approximately one cell generation; the second, after approximately 2.5 cell generations. It is evident that the first and second cell generations produced in the absence of external nitrogen are markedly altered in their capacity to grow and

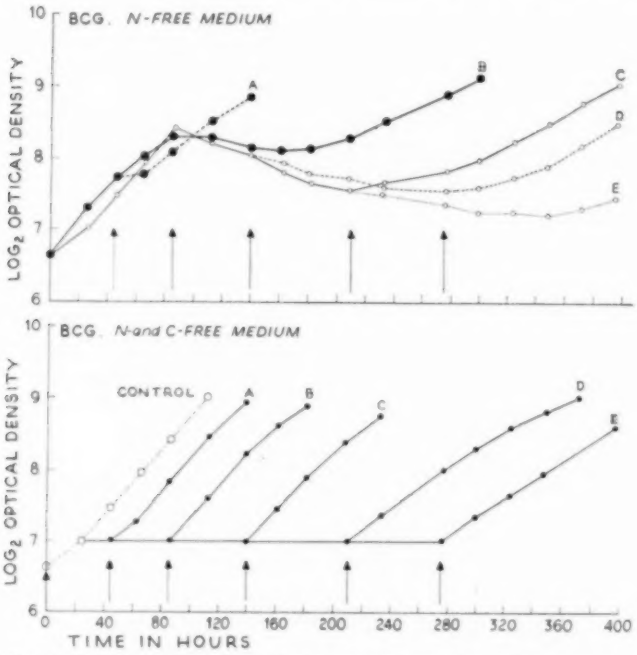

FIG. 2. Growth of BCG after nitrogen and nitrogen plus carbon starvation.

presumably, therefore, in their ability to utilize external nitrogen. This alteration may be correlated with the reduction in the amount of nitrogen per cell (table 1). The results thus suggest that during this period there is a conversion of nitrogen from the enzyme systems involved in the synthesis of cellular nitrogenous substances from the NH_4Cl of the medium to other enzymes capable of splitting cellular nitrogenous substances.

The increase in generation time observed after the cultures were subjected to either nitrogen or nitrogen and carbon starvation may be understood in terms of the hypothesis given above. The increase occurs after approximately five days'

starvation; that is, at the time it is postulated that some of the enzymes involved in the utilization of NH_4Cl have been converted biologically to other enzymes capable of utilizing cellular nitrogenous substances. Cells so equipped might be expected to grow more slowly than those of the original culture. If this interpretation is correct, it would be expected that after a few transfers in a medium containing NH_4Cl as the nitrogen source, the original generation time would be restored. Although these experiments have not yet been performed, the present experiments do raise a question concerning the significance of the term "adaptive enzyme," i.e., should those enzymes which enable the organism to utilize NH_4Cl be considered "adaptive" or should those which enable it to utilize intracellular nitrogenous substances be so designated? At present the decision would seem to depend largely on the experimental habits of the investigator rather than on the intrinsic constitution of the organism investigated. Regardless of theory, the difference between H37Rv and BCG in this respect is very striking and seems worthy of further investigation.

The results have an obvious bearing on the preparation and preservation of BCG vaccines. It would seem preferable that, in the final growth phase, the carbon source and not the nitrogen source should be present in limiting amounts and that all sources of carbon should be eliminated from the final suspension medium. It also seems of value to re-examine the technology of tuberculin production in the light of the lysis phenomenon here described.

SUMMARY

In the presence of adequate amounts of glucose in a medium deficient in a source of nitrogen, tubercle bacilli continue to proliferate.

The cells of the second generation (fourth day) produced under these conditions have a nitrogen content per milligram of dry weight which is only approximately 40 per cent of the cells used as inoculum. Relatively little of the cellular nitrogen originally added is lost to the medium.

Cells surviving to the fifteenth day under these conditions also show a reduction in nitrogen per milligram of dry weight to 40 per cent, while the total cellular nitrogen is reduced to approximately 50 per cent of the amount originally present. This is a reflection of the lysis previously described.

In the absence of both carbon and nitrogen sources in the medium, there is only a slight reduction in nitrogen per milligram of dry weight and total nitrogen at the end of fifteen days. This is correlated with the absence of lysis under these conditions.

The first and second cell generations produced in the presence of external glucose and absence of nitrogen are so altered that a lag period ensues before growth is resumed on the addition of nitrogen. This is attributed to a loss of enzymes involved in the assimilation of nitrogen from the medium and the substitution therefore of enzymes capable of acting upon cellular nitrogenous substances.

BCG differs from H37Rv in the type of growth observed after nitrogen starvation. The former shows a marked increase in generation time, while in the latter this increase is relatively slight.

SUMARIO

Comparación del Crecimiento y de la Autólisis de Dos Cepas de Bacilos Tuberculosos

En presencia de cantidades adecuadas de glucosa en un medio deficiente en una fuente de nitrógeno, los bacilos tuberculosos continúan proliferando.

Las células de la segunda generación (cuarto día), producidas en esas condiciones muestran un contenido de nitrógeno por miligramo en peso seco que sólo representa aproximadamente 40 por ciento de las células usadas como inóculo. Relativamente, se pierde poco del nitrógeno celular agregado primitivamente al medio.

Las células que sobreviven hasta el décimoquinto día en esas condiciones muestran también una reducción a 40 por ciento del nitrógeno por miligramo en peso seco, mientras que el nitrógeno celular total total desciende aproximadamente a 50 por ciento de la cantidad presente primitivamente. Esto refleja la lisis previamente descrita.

En ausencia de fuentes tanto de carbono cuanto de nitrógeno en el medio, sólo hay una leve reducción del nitrógeno por miligramo en peso seco y del nitrógeno total al cabo de quince días. Esto se correlaciona con la falta de lisis en dichas condiciones.

La primera y la segunda generaciones de células producidas en presencia de glucosa externa y ausencia de nitrógeno están tan alteradas que, al agregar nitrógeno, sobreviene un período de demora antes de reanudar el crecimiento. Esto se imputa a la pérdida de encimas impuesta por la asimilación del nitrógeno del medio y al reemplazo de los mismos por encimas capaces de obrar sobre las substancias nitrogenadas de las células.

El BCG discrepa del H37Rv en la forma de crecimiento observada después de la privación de nitrógeno. El primero muestra decidido aumento en el tiempo de generación, en tanto que en el segundo ese aumento es relativamente escaso.

RESUME

Comparaison de la croissance et de l'autolyse de deux souches de bacille tuberculeux

En présence d'une quantité adéquate de glucose dans un milieu privé d'une source d'azote, les bacilles tuberculeux ont continué à proliférer.

Dans les cellules de seconde génération (quatrième jour) produites dans ces conditions, la valeur du contenu en azote par milligramme de poids sec n'est que d'environ 40% par rapport aux cellules utilisées comme inoculum. La quantité d'azote cellulaire initialement ajouté qui passe dans le milieu est relativement faible.

Dans les conditions de l'expérience, les cellules qui survivent jusqu'au quinzième jour montrent une réduction de leur teneur en azote par milligramme de poids sec pouvant atteindre 40%, tandis que la valeur de l'azote total de la cellule s'abaisse jusqu'à environ 50% par rapport à la quantité initiale. Ceci est le résultat de la lyse précédemment décrite.

En l'absence de sources de carbone et d'azote dans le milieu, on n'observe qu'une légère réduction de la quantité d'azote par milligramme de poids sec et de l'azote total, à la fin de la période de quinze jours. Ceci est en corrélation avec l'absence de lyse dans ces conditions.

La première et la seconde génération de cellules produites quand le glucose est présent dans le milieu et l'azote absent sont tellement altérées, qu'il y a une période d'arrêt avant que la croissance ne reprenne sous l'influence d'addition d'azote. Ce phénomène est attribué à la perte des enzymes intéressés dans l'assimilation de l'azote du milieu et, par voie de conséquence, par l'apparition d'enzymes capables d'agir sur les composés azotés cellulaires.

Le BCG diffère de l'H37Rv par le type de croissance observé après la privation d'azote. Le premier montre une augmentation de la vitesse de reproduction tandis que, chez l'autre, cette augmentation est relativement faible.

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THE MONALDI PROCEDURE[1]

A Report of Thirty Cases

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(Received for publication July 19, 1951)

INTRODUCTION

A thorough review of the Monaldi procedure in tuberculosis was presented in 1948 by Woodruff, Kelley, and Stranahan (1). Since that time, little has appeared in the literature on this subject. Woodruff, in January 1950, reported follow-up observations on his series. Monaldi (2) recently restated his views, namely, that endocavitary drainage may be used either prior to thoracoplasty or following thoracoplasty if residual cavity is present. He emphasized the fact that drainage alone will permanently close cavities in some instances.

The present report is an analysis of the experience with the Monaldi procedure at the Connecticut State sanatoriums from October 1946 to February 1951. The procedure was attempted thirty-three times on 30 patients. Because of the complications listed in table 1, the procedure was abandoned in 6 patients; in some instances, after two unsuccessful attempts had been made. More than one cavity was drained in only one patient who had two procedures.

The indications for Monaldi drainage in the present series were similar to those previously published (1). It was employed in patients with giant cavity, either for palliation, in the hope that the patient's condition would improve sufficiently to permit thoracoplasty or resection, or for reduction in size of the cavity to permit smaller thoracoplasty. It is believed that cavity closure following endocavitary drainage alone should be secured by permanent collapse measures.

Contraindications included history of hemorrhage, free pleural space, and cavity which was inaccessible or too small to enter. A relative contraindication is lower lobe cavity, since it must be reached usually from behind where the scapula tends to interfere with proper functioning of the catheter and where the fistula is within the operative field of possible future thoracoplasty or thoracotomy. To this list of contraindications should be added residual cavity under thoracoplasty since such cavities are notoriously difficult to locate and frequently lie close to large vessels which can be the source of fatal hemorrhage.

PROCEDURES

In the present series, anterior thoracoplasty, according to the method of Haight (3), has invariably preceded insertion of the catheter. During the operative procedure, the pleura was inspected through the bed of the rib or cartilage overlying the cavity and, if found free, was treated with powdered sulfonamide or talc to promote the formation of adhesions. Subsequently, the Monaldi procedure was performed essentially according to the method previously described

[1] From Uncas-on-Thames Sanatorium, Norwich, Connecticut.

(1). Posterolateral thoracoplasty was performed in 19 patients. Monaldi drainage was supplemented by phreniclasis in 4 patients. Resection was performed on 4 patients, 2 of whom had posterolateral thoracoplasty and are also included in the 19 noted above. Two patients, upon whom the Monaldi procedure was unsuccessful, subsequently had open cavernostomy.

A day or so after the insertion of the catheter, minus 20-centimeter suction was cautiously instituted, and, if no bleeding resulted, suction was continued without interruption. The apparatus employed has been described by Woodruff (4). The criteria for terminating endocavitary drainage are not well established. It is believed, however, that the catheter may be withdrawn gradually after the sputum and drainage have been negative for acid-fast bacilli for several months

TABLE 1

REASONS FOR ABANDONMENT OF CATHETERIZATION

Thirty Patients with Monaldi Drainage

COMPLICATION	NUMBER OF PROCEDURES	NUMBER OF PATIENTS
Pneumothorax	4	2
Pneumothorax (followed by empyema)	2	2
Hemorrhage	1	1
Respiratory stridor (unexplained)	1	1

TABLE 2

ADDITIONAL COMPLICATIONS

Thirty Patients with Monaldi Drainage

PREDISPOSING PROCEDURE	POSTOPERATIVE SPREAD OF DISEASE	WOUND INFECTION (ABSCESS)	EMPYEMA AND LATE BRONCHOPLEURAL FISTULA
Anterior thoracoplasty	4	0	0
Intubation (Monaldi)	4	3	1*
Posterolateral thoracoplasty	4	0	0
Resection	0	0	1

* At the time of later pulmonary resection, a thrombus was found in the pulmonary artery.

and roentgenograms reveal no evidence of residual cavity. In the present series, the shortest and longest periods of catheter drainage were 67 and 813 days, respectively, with an average of 379 days. After removal of the catheter, healing of the sinus has been prompt except when residual cavitation remains.

RESULTS

Each of the 30 patients selected for the Monaldi procedure had giant cavity by roentgenographic examination. Four of these patients had cavity in the contralateral lung. Endocavitary pressures recorded in 27 instances at the time of catheterization were as follows: 20, positive; 3, negative; and 4, neutral. Seven patients were febrile before endocavitary drainage, and none of these patients

demonstrated appreciable defervescence after the procedure. Although exact measurements are not available, it is believed that the amount of sputum has

TABLE 3

CAUSES OF DEATH

Thirty Patients with Monaldi Drainage

	NUMBER OF DEATHS	LENGTH OF TIME AFTER MONALDI DRAINAGE
		Months
Pulmonary resection	2	35 15
Progressive disease	3	7 13 48
Postoperative "pneumonia"	1	13
Late bronchopleural fistula and progression of disease	1	6
Total number of deaths	7	
Average length of time after Monaldi drainage		19½

TABLE 4

PRESENT STATUS OF THE THIRTY PATIENTS ACCORDING TO PROCEDURES PERFORMED

	AFTER MONALDI DRAINAGE	AFTER MONALDI DRAINAGE PLUS POSTERO-LATERAL THORACOPLASTY	AFTER MONALDI DRAINAGE PLUS PHRENICLASIS	AFTER RESECTION	AFTER THORACOPLASTY AND CAVERNOSTOMY
Lost to follow-up	0	0	1	0	0
Cavity closed by laminagram	0	6	0	—	1
Cavity closed by routine postero-anterior roentgenogram only	0	5†	0	2	0
Sputum negative for tubercle bacilli	2	12†	0	2	2
Lesion, "inactive" (NTA 1950 classification)	0	10†	0	2	0
Contralateral cavity present	1	1	0	0	1
Disease progressing	0	0	1	0	0
Died	1	4†	1	2	0
Total in group	4*	19‡	3	4	2

* Three of these patients still have catheters in place.

† One of these patients is also included in the resection group.

‡ Two of these had later resections and are also included in the resected group. One patient had phreniclasis in addition to thoracoplasty and Monaldi drainage.

decreased with endocavitary drainage. Decrease in the size of the cavity on the roentgenogram was noted in 23 of the 26 cavities which were successfully drained.

Complications not included in table 1 are included in table 2. Those patients

who died are again listed in table 3. Seven deaths occurred in this group of 30 patients, a case mortality of 23 per cent.

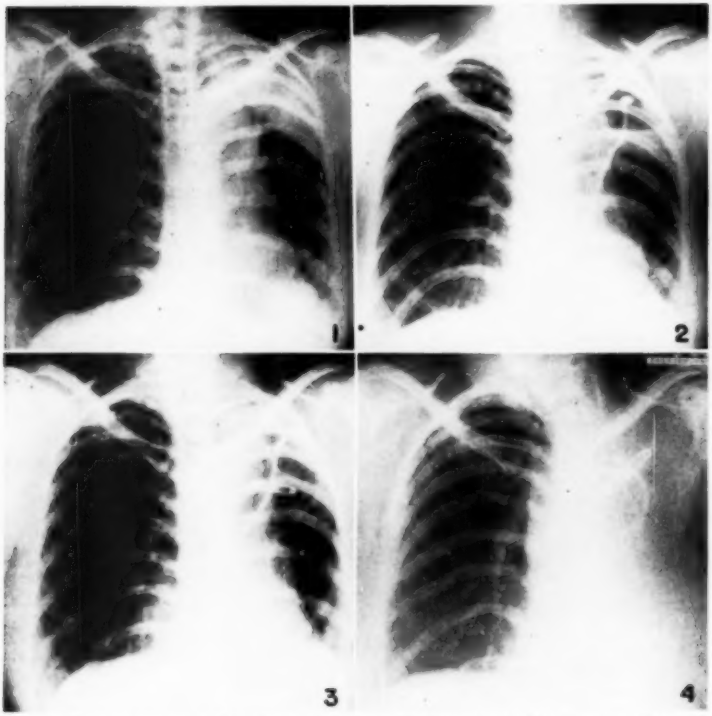

FIG. 1. Roentgenogram of patient with large filled cavity in the upper portion of the left lung. Sputum negative for tubercle bacilli at the time of this film.

FIG. 2. Roentgenogram of same patient immediately following Monaldi operation. Much purulent material was removed upon insertion of catheter. Cavity still large.

FIG. 3. Roentgenogram of same patient three months following insertion of Monaldi catheter. Cavity contracting to some extent but not closed.

FIG. 4. Same patient following extensive thoracoplasty, left. Satisfactory collapse of lung, including cavity at the apex. The Monaldi catheter remains in place. Cavity not definitely visualized. Subsequently, catheter was removed and there has been complete healing of the tract.

Table 4 summarizes the status of the 30 patients who were chosen for the Monaldi procedure. The cases are arranged according to the type of operative procedure performed. Since 2 of the resections were performed on patients who had previously had Monaldi and posterolateral thoracoplasty with failure, they are included under both headings. It is interesting to note that in this series the

Monaldi procedure plus anterior thoracoplasty alone cured no one. The best results were obtained when the Monaldi procedure was supplemented by postero-lateral thoracoplasty.

When Monaldi operation and thoracoplasty failed to close cavity and control disease, it was not possible in all cases to perform any other procedure because of extensive involvement of lungs and poor condition of the patient. Resection was performed in 4 patients. The 50 per cent case mortality in this group is understandable when one considers the poor condition of the patients.

Streptomycin was employed in variable amounts in 17 cases. It is believed, however, that no conclusions can be drawn regarding the efficacy of this drug in such a small series. Penicillin was used routinely for approximately one week following insertion of the Monaldi catheter. The low incidence of wound abscess (table 2) indicates the efficacy of this treatment.

SUMMARY

A review of 30 patients who were subjected to the Monaldi procedure is presented. The mortality for the whole group is 23 per cent. There has been, in addition, a relatively high morbidity, which probably is attributable to the severity of the disease. Whenever possible, the Monaldi procedure should be followed by thoracoplasty or resection.

SUMARIO

El Procedimiento de Monaldi, Presentación de Treinta Casos

Esta reseña comprende 30 enfermos sometidos al procedimiento de Monaldi. La mortalidad para todo el grupo llegó a 23 por ciento. Hubo además una morbidad relativamente alta, lo cual es imputable probablemente a la gravedad de la dolencia. Siempre que sea posible, el procedimiento de Monaldi debe ir seguido de la toracoplastia o la resección.

RESUME

Procédé de Monaldi. Un rapport sur trente cas

Les observations de 30 malades soumis au procédé de Monaldi sont passées en revue. La mortalité pour la totalité du groupe est de 23%. De plus il y a été observé une morbidité relativement élevée qui est probablement attribuable à la gravité de l'affection. Chaque fois que cela sera possible, le procédé de Monaldi devra être suivi d'une thoracoplastie ou d'une résection.

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LINEAR BASAL ATELECTASIS FOLLOWING THERAPEUTIC PHRENIC NERVE INTERRUPTION[1]

RICHARD P. JAHN AND JOHN K. OLINGER

(Received for publication August 17, 1951)

INTRODUCTION

Following phrenic nerve interruption in the treatment of pulmonary tuberculosis, linear roentgenographic shadows occasionally appear above the paralyzed hemidiaphragm. The appearance of similar shadows has been noted secondary to a variety of conditions associated with pulmonary hypoventilation due to splinting of the diaphragm. Since the work of Fleischner in 1936, these lesions have been recognized as areas of linear or "plate-like" atelectasis. Thus far, the literature has contained little mention of the appearance of this phenomenon following phrenic nerve paralysis in the treatment of pulmonary tuberculosis. The present study is a review of roentgenograms of patients with phreniclasias, with particular reference to the subsequent appearance of linear shadows above the paralyzed diaphragm.

OBSERVATIONS

Three hundred and sixty-one therapeutic phrenic nerve interruptions were performed at Muirdale Sanatorium from January 1942 to January 1949. Of this group, 293 cases with satisfactory serial roentgenograms form the basis of this study. In 23 cases, characteristic linear basal shadows were demonstrable. Usually, the shadows appeared on roentgenograms taken three months following phreniclasia and persisted from four months to more than five years. With the resumption of diaphragmatic motion, the opacities usually disappeared, but occasionally persisted as fine lines. In some cases, the shadows disappeared before the return of diaphragmatic function. In all but 2 cases, the linear shadows appeared in areas of the lung which had previously shown no roentgenographic evidence of active pulmonary disease.

Morphologically, the shadow is commonly seen in the postero-anterior roentgenographic view as a single, horizontal, linear density a few centimeters above the paralyzed diaphragm (figure 1). In length, the opacity usually measures five to seven centimeters, but occasionally it extends from the mediastinal border to the lateral margin of the lung. In its early development, the margin of the density may be hazy in outline and as broad as two centimeters (figure 2). Later, the shadow is sharply demarcated, a few millimeters in thickness. At times, its appearance resembles thickened interlobar fissure, differing only in its position and anatomic relationships. Variations in appearance frequently are noted, e.g., multiple linear shadows (figure 3), oblique and curved lines. The density may appear in the air bubble of the stomach. On fluoroscopic examination, the "plate-like" nature of the lesion can be demonstrated by shifting the patient's

[1] From Muirdale Sanatorium, Milwaukee, Wisconsin.

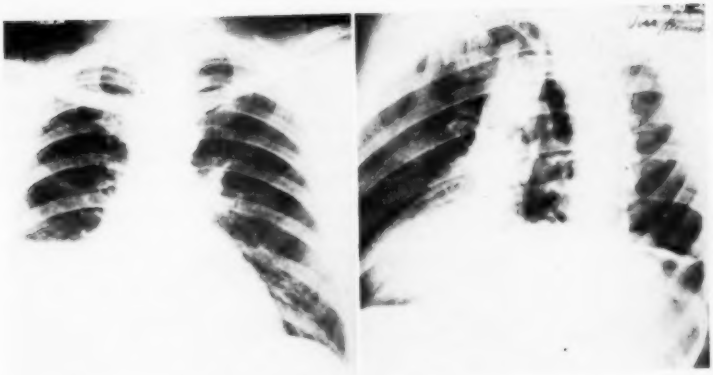

FIG. 1. (Left) Linear atelectasis as it appears in the roentgenograms, postero-anterior projection. (Right) The linear nature of the atelectasis may be seen in the oblique view.

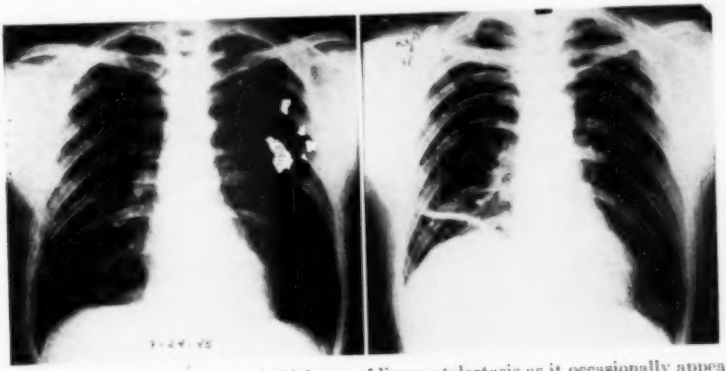

FIG. 2. The curved nature and thickness of linear atelectasis as it occasionally appears in the postero-anterior roentgenograms.

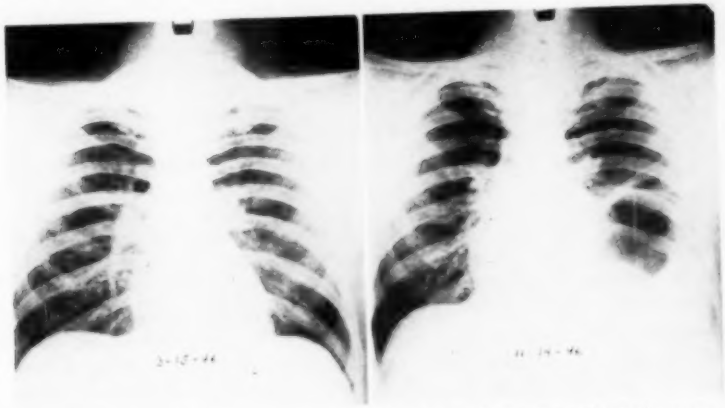

FIG. 3. Postero-anterior roentgenograms showing multiple fine atelectatic areas.

position in forward and backward inclination. In some instances, tomographic studies showing a considerable antero-posterior diameter further suggested the disc-like morphology of the density. Pressure changes in the lung established by employing the Valsalva maneuver had no effect which could not be attributed to positional changes.

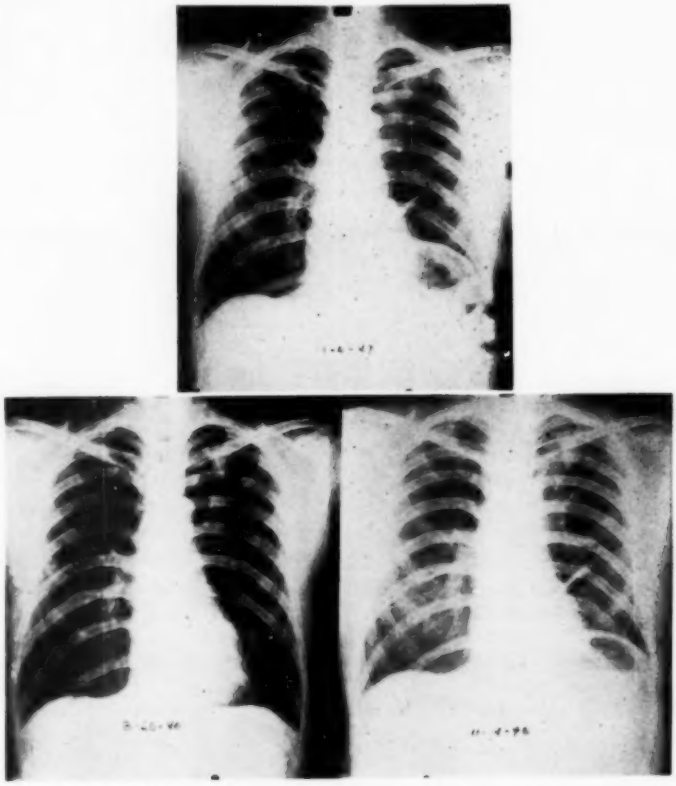

FIG. 4. Linear opacity from which anatomic specimen showed changes suggesting old atelectasis.

A pathologic specimen was obtained following pneumonectomy in the case illustrated in figure 4. An area of lung tissue, measuring 5 cm. by 3 cm. by 3 mm., containing obliterated blood vessels and bronchioles, compressed and surrounded by fibrosis definitely suggesting antecedent atelectasis, was found in this specimen. Since a thoracoplasty had been performed in the interval between the last roentgenographic evidence of linear atelectasis and the pneumonectomy, definition of the exact anatomic relationship was difficult.

Hence, irrefutable evidence that the anatomic lesion and the shadow on the roentgenogram were identical was lacking.

DISCUSSION

While the absence of adequate pathologic specimens precludes a definite statement concerning the precise nature of this linear roentgenographic opacity following phreniclasia, it is reasonable to surmise that at inception this shadow is similar, if not identical, to the "plate-like" atelectasis described by Fleischner in 1936 (1, 2, 3). Fleischner and, later, Oppenheimer (4) showed that, in circumstances causing marked hypoventilation of the lung, small areas of atelectasis may appear. The mechanism by which this lesion occurs is postulated as an interference with normal bronchial drainage and subsequent obstruction of some of the smaller bronchioles.

"Fleischner's atelectasis" has been reported coincident with a number of conditions, including subdiaphragmatic abscess, ruptured abdominal viscera, acute appendicitis, acute cholecystitis, portal cirrhosis, severe contusions to the chest wall, and extreme inanition (4, 5, 6). So frequently has this roentgenographic finding been associated with intra-abdominal pathology that Marks and Nathan (6) have called it "the linear atelectatic sign in intra-abdominal disease." The etiologic mechanism suggested by Fleischner and Oppenheimer as pulmonary hypoventilation (due to splinting of the diaphragm) would appear to be operative in all of these conditions.

The present writers can add little to Fleischner's concept of the pathogenesis of linear atelectasis. It was of interest, however, to review a series of cases treated with pneumoperitoneum at Muirdale Sanatorium during this same period. Pneumoperitoneum without phreniclasia conspicuously failed to produce basal linear roentgenographic shadows, even with a very marked rise of the diaphragm. Moreover, maximum breathing capacity determinations, which may show a decrease of as much as fifteen liters following phreniclasia, rarely showed a decrease of more than five liters after pneumoperitoneum.

SUMMARY

Approximately 10 per cent of a series of 293 patients who received therapeutic phrenic nerve interruption for treatment of pulmonary tuberculosis presented linear, basal, roentgenographic opacities above the paralyzed hemidiaphragm. In the absence of antecedent roentgenographic evidence of active tuberculosis in the areas involved, these shadows appeared to represent segmental (linear) atelectasis. With resumption of diaphragmatic motion, the opacities usually disappeared, but occasionally persisted as fine lines. The similarity in appearance and probable pathogenesis between these shadows and the "plate-like" atelectasis of Fleischner is discussed.

SUMARIO

Atelectasia Basal Lineal Consecutiva a Interrupción Terapéutica del Frénico

En esta serie, aproximadamente 10 por ciento de los enfermos en que se ejecutó la interrupción terapéutica del frénico para el tratamiento de la tuberculosis pulmonar, presentaron

radiográficamente opacidades basales, lineales, más arriba del hemidiafragma paralizado. A falta de previos datos radiológicos de tuberculosis activa en las zonas afectadas, esas imágenes parecen representar atelectasia segmental (lineal). Al reanudarse el movimiento diafragmático, dichas opacidades suelen desaparecer, pero a veces persisten en forma de líneas tenues. Discutése la semejanza en aspecto y probable patogenia entre dichas sombras y la atelectasia "laminada" de Fleischner.

RESUME

Atélectasie linéaire basale par interruption thérapeutique de la fonction du nerf phrénique

Dans cette série, chez environ 10% des malades chez lesquels l'interruption thérapeutique de la fonction du nerf phrénique avait été effectuée pour traiter la tuberculose pulmonaire, des ombres linéaires basales situées au-dessus de l'hémidiaphragme paralysé ont été observées sur les radiogrammes. En l'absence de preuves radiologiques antérieures de l'existence d'une tuberculose pulmonaire en activité dans la région intéressée, ces ombres paraissent représenter une atélectasie segmentaire (linéaire). La disparition de ces ombres succède en général à la reprise de fonction du diaphragme; ces ombres persistent parfois sous la forme de lignes fines. L'analogie de l'aspect de ces ombres et l'atélectasie "en plaque" de Fleishner ainsi que leur pathogénie probable, sont étudiées.

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Case Reports

RECURRENT LARYNGEAL NERVE PARALYSIS AS A COMPLICATION OF PULMONARY TUBERCULOSIS[1]

A Report of Two Cases

DAVID B. RADNER AND GORDON L. SNIDER

(Received for publication August 14, 1951)

Paralysis of the recurrent laryngeal nerve due to tuberculous involvement of mediastinal structures is a rare although accepted entity; however, there is a paucity of clinical reports of this condition in the literature (1, 2, 3, 4). Because of the infrequency of this condition and the interest in recent years in the association of bronchogenic carcinoma and pulmonary tuberculosis, it seemed of value to report two additional cases.

CASE REPORTS

Case 1. A white male tailor was admitted to this Sanatorium for the first time in 1932 at the age of thirty-four because of cough, expectoration, fever, and hemoptysis. A diagnosis was made of pulmonary tuberculosis, moderately advanced, bilateral, active. The sputum was positive for acid-fast organisms. The patient was discharged with an arrested lesion two years later, at which time the sputum was negative for tubercle bacilli. He was subsequently hospitalized five times in various tuberculosis hospitals for the treatment of reactivated disease with recurrence of hemopytsis and sputum positive for tubercle bacilli. During his fifth admission he developed hoarseness following a grippe-like illness in April 1947. Repeated laryngeal examinations prior to this time revealed no laryngeal disease and normally functioning vocal cords. In April 1947, it was first noted that the left vocal cord did not move and remained in the mid or cadaveric position. It has remained so ever since. Bronchoscopic examination on May 16, 1951 revealed considerable shortening and distortion of the trachea and main bronchi, with marked retraction of the left main bronchus superiorly. Neither endobronchial tuberculosis nor bronchial neoplasm was found. Cytologic examination of aspirated material was negative for tumor cells. A review of chest films dating back to 1944 indicated the presence of chronic fibrocaseous tuberculosis involving both upper lung fields, with an area of increased density obscuring the arch of the aorta. In April 1947, at the time of the appearance of the left recurrent nerve paralysis, the density had shown little change except for a slight retraction superiorly. In the ensuing year the mass showed an increase in density and sharper definition in its margins. Further apical retraction of the mass has occurred since 1947. Tomographic roentgenograms of the left upper lobe disclosed a dense homogeneous mass distinct from the aortic arch, with evidence of marked apical retraction of the left hilus (figures 1, 2, 3, 4).

Case 2. A white male communications engineer was first treated for moderately advanced pulmonary tuberculosis in 1938 at the age of thirty-one. His pulmonary lesion was described as a tuberculous pneumonia of the right upper lobe, and sputum was positive for acid-fast organisms. He was treated on bed rest at home for ten months, followed by limited activity

[1] From Winfield Hospital, Winfield, Illinois.

for another six months. He returned to work but was not under medical supervision. In 1949 he first noted some hoarseness and "cracking of his voice." This lasted for almost two months but eventually cleared with return of normal voice. In January 1950, he noted the return of hoarseness which was diagnosed and treated as acute laryngitis. After several

Case 1

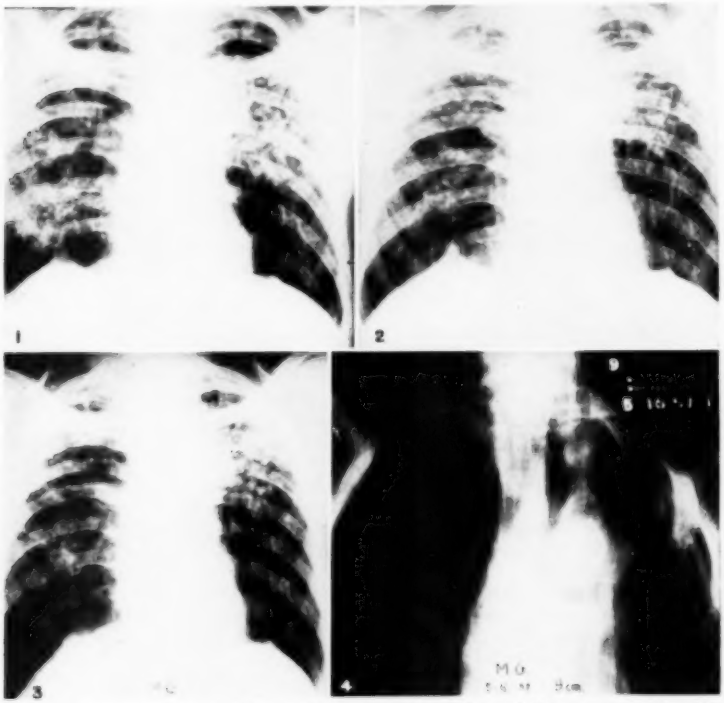

FIG. 1. Roentgenogram of chest, February 25, 1944. Bilateral fibrocaseous tuberculosis with mass obscuring arch of aorta.

FIG. 2. Roentgenogram of chest, December 11, 1947, eight months after onset of left recurrent laryngeal nerve paralysis. The mass is denser and more sharply circumscribed.

FIG. 3. Roentgenogram of chest, March 13, 1951. The mass persists and the left hilus shows further retraction toward the apex.

FIG. 4. Tomographic roentgenogram of chest, May 16, 1951, 9 cm. anterior to vertebral spines. A dense homogeneous mass can be distinguished from the arch of the aorta by the calcification in the latter.

moderate hemoptyses a chest roentgenogram was taken, and active pulmonary tuberculosis was again diagnosed. Laryngoscopy and bronchoscopy, performed in February 1950, revealed paralysis of the left vocal cord, with marked retraction of the left main bronchus superiorly. There was no evidence of laryngeal or endobronchial tuberculosis. No bronchogenic tumor was found; cytologic examination of aspirated material was negative for

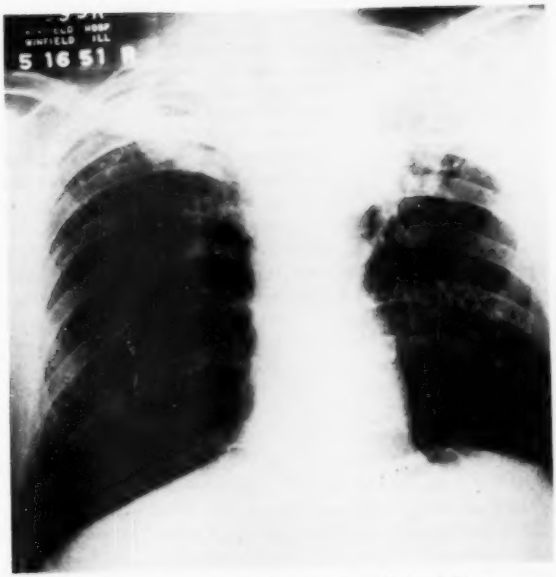

FIG. 5. Roentgenogram of the chest, May 16, 1951, bilateral fibrocaseous tuberculosis is present. A dense homogeneous shadow overlies the aortic arch on the left. Both hila are retracted superiorly.

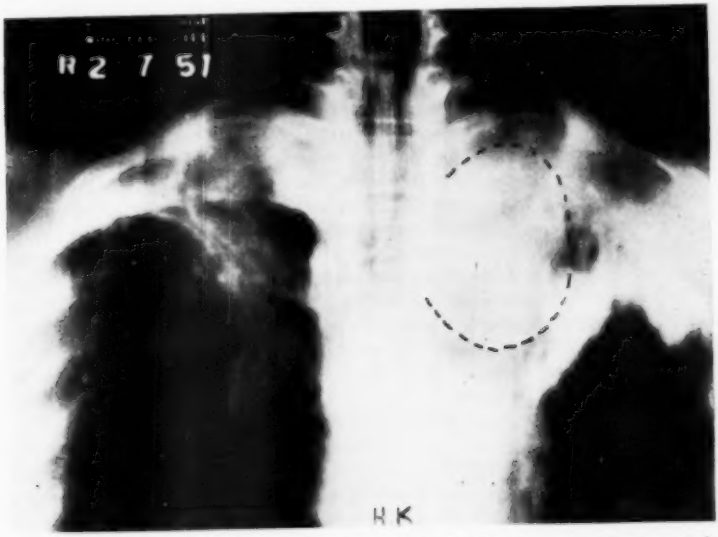

FIG. 6. Tomographic roentgenogram of chest, May 16, 1951, 9 cm. anterior to vertebral spines. There is a large homogeneous mass in the region of the aortic arch.

tumor cells. He was admitted to the Sanatorium on April 11, 1950, where the above findings were confirmed. The earliest chest roentgenogram available for comparison was dated March 1950. This and subsequent films disclosed bilateral fibrocaseous tuberculosis, more extensive on the left where a dense homogeneous shadow was seen overlying the aortic arch. Follow-up films have revealed clearing of the peripheral portions of the lesions, with considerable apical retraction of the left upper density. Tomographic roentgenograms of the left upper lung field revealed a large homogeneous density distinct from the aortic arch (figures 5 and 6).

DISCUSSION

The commonest type of unilateral vocal cord paralysis is due to involvement of the recurrent laryngeal nerve. Pathologic processes in the neck involve both nerves with equal frequency, the largest number of cases resulting from goiter or thyroid surgery. It is generally agreed that within the thorax the left recurrent laryngeal nerve is involved more often than is the right nerve (5). This difference can be explained by the difference in the anatomic relationship on the two sides. The right recurrent laryngeal nerve arises at the level of, and just anterior to, the right subclavian artery, winds around it posteriorly, and is there in contact with cervical pleura. It then ascends between the trachea and esophagus, entering the larynx at the lower border of the cricoid cartilage. The left nerve arises from the vagus at the level of, and anterior to, the arch of the aorta. It winds around the ligamentum arteriosum passing through a triangle made up by the aorta, ligamentum arteriosum, and the pulmonary artery. It then ascends alongside the trachea, more anteriorly than the right nerve, entering the cricoid cartilage similarly to the right branch. Rouviere (6) states that a lymph node of the left tracheobronchial group is not uncommonly found in relation to the left recurrent nerve in the triangle discussed above. He has called this node "the node of the loop of the left recurrent nerve." One of the nodes of the left anterior mediastinal chain is also quite commonly found on the anterior aspect of the ligamentum arteriosum (node of the obliterated ductus arteriosus—Rouviere) (figure 7). Grant (7) also makes mention of the presence of tracheobronchial lymph nodes in the triangle bounded by the aorta, ligamentum arteriosum, and the pulmonary artery.

It is therefore obvious that the more frequent involvement of the left recurrent nerve is a result of its more intimate relationship with intrathoracic structures commonly involved by disease. This would explain the unilateral vocal cord paralysis resulting from aortic aneurysm or carcinoma of the esophagus. The explanation is less obvious in paralysis which occurs with bronchogenic carcinoma, heart disease, and tuberculosis unless the importance of the lymph nodes adjacent to the left nerve is recognized. The involvement of these nodes with carcinoma metastatic from the bronchus or breast readily explains the resultant paralysis of the left recurrent nerve in these conditions (figure 7). Dolowitz and Lewis (8) express the opinion that cardiac hypertrophy, with or without pulmonary artery engorgement, is insufficient to produce left recurrent laryngeal palsy unless there is associated enlargement of the left tracheobronchial lymph nodes.

Most authors have recognized mediastinal tumors and enlarged mediastinal, paratracheal, and bronchial nodes as a cause for left recurrent laryngeal nerve paralysis. Despite the frequency with which the mediastinal and tracheobronchial nodes are involved in tuberculous infection, paralysis of the recurrent nerve is relatively uncommon in tuberculosis. The same nodes which are involved with carcinoma much more frequently involve the nerve. It has been noted that abscess formation in the lymph nodes adjacent to the nerve leads to paralysis (9). Considering the large number of cases of primary tuberculosis with involvement of paratracheal and bronchial nodes, reports of vocal

cord paralysis should be more frequent in the literature. The report of Castells (4) of a case of primary tuberculosis producing recurrent paralysis is one of very few. He points out, however, that on tomographic study there was some evidence of central breaking down in the nodes and that on bronchoscopy there was endobronchial involvement with tuberculosis in the adjacent bronchus. This would again speak for the necessity of abscess formation in the involvement of the recurrent nerve. Tuberculous involvement of the lymph nodes adjacent to the left recurrent nerve obviously does not result in paralysis in most instances since most tuberculous nodes do remain intact. When the lymph gland gives rise to a cold abscess, however, the nerve may be paralyzed. Retraction of the left upper lobe bronchus toward the apex may permit the development of paralysis with less lymph node involvement.

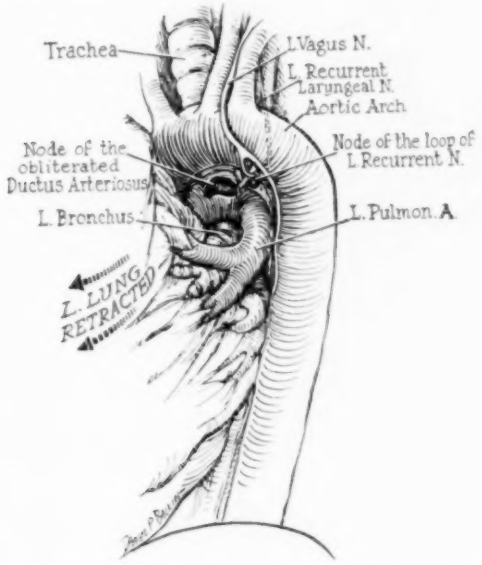

FIG. 7. Anatomic relationship of the left recurrent laryngeal nerve with lymph nodes in the triangle formed by the aortic arch, the ligamentum arteriosum, and the pulmonary artery.

Involvement of the right recurrent nerve has been recorded, although less frequently, than that of the left nerve. In Arnstein's (1) series, the right nerve was involved twice; the left, 47 times. In Portmann's review (3), the right was involved twice; the left, 14 times. The right nerve is usually involved by disease in the apex of the lung from which it is separated only by the pleura (10, 11).

The two cases described in the present report have many features in common. In both instances, the paralysis of the left recurrent nerve occurred after chronic pulmonary tuberculosis of long duration, fifteen and eleven years, respectively. In both cases a dense mass, presumably caseous, developed in the region of the aortic arch, and marked apical

retraction of the left upper lobe bronchus ensued. In both cases, bronchogenic carcinoma complicating tuberculosis was considered. This was excluded by bronchoscopic and cytologic study. One of the patients (Case 1) has been observed for more than four years and the other (Case 2), for more than eighteen months, without evidence of tumor.

SUMMARY

Two cases of left recurrent laryngeal nerve paralysis occurring in the course of chronic pulmonary tuberculosis are presented. Both patients were studied by direct laryngoscopy, bronchoscopy, and tomography. Bronchogenic carcinoma was considered in both cases and reasonably excluded by bronchoscopic and cytologic studies, with confirmation by follow-up observations of more than four years and one and one half years, respectively. The pathogenesis of left recurrent laryngeal nerve paralysis is briefly discussed, and the importance of the relation of the left tracheobronchial lymph nodes to the left recurrent nerve is emphasized.

SUMARIO

Parálisis del Nervio Laríngeo Recurrente como Complicación de la Tuberculosis Pulmonar

Preséntanse 2 casos de parálisis del nervio laríngeo inferior izquierdo, sobrevenida en la evolución de una tuberculosis pulmonar crónica. Ambos fueron estudiados con la laringoscopia directa, la broncoscopia y la tomografía. En los dos, se pensó en carcinoma broncógeno, excluyéndose convincentemente por los estudios broncoscópicos y citológicos, y confirmándose por la observación subsiguiente durante más de cuatro años y uno y medio años, respectivamente. Discutida brevemente la patogenia de la parálisis del nervio laríngeo recurrente izquierdo, recálcase la importancia de la relación de los ganglios tráqueobronquiales izquierdos con el mismo.

RESUME

Paralysie du nerf récurrent comme complication de la tuberculose pulmonaire

Présentation de deux cas de paralysie du nerf récurrent gauche survenue au cours de la tuberculose pulmonaire chronique. Ces deux cas ont été étudiés par laryngoscopie directe, bronchoscopie et tomographie. Le diagnostic de cancer bronchiogénique a été considéré dans ces deux cas, il a été exclus d'une part par des examens bronchoscopiques et cytologiques adéquats, et d'autre part par la mise en observation des malades pendant plus de quatre ans dans un des cas, et un an et demi dans l'autre. La pathogénèse de la paralysie du nerf récurrent du pneumogastrique est brièvement étudiée; l'importance des rapports entre les ganglions trachéobronchiques gauche et le récurrent gauche est mise en évidence.

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American Trudeau Society

Medical Section of the National Tuberculosis Association

Reports of the Clinical and Laboratory Subcommittees of the Committee on Medical Research

CLINICAL SUBCOMMITTEE

The Clinical Subcommittee has held three meetings during the year as follows: (*1*) November 14 and 15, 1950, New York, N. Y., (*2*) January 26, 1951, Atlanta, Georgia, (*3*) May 13, 1951, Cincinnati, Ohio.

A portion of the November and May meetings was devoted to a joint session with the Laboratory Subcommittee. The report of the November meetings was circulated to members of the two Subcommittees, the Committee on Medical Research and the American Trudeau Society Council and chairmen of committees, to executive secretaries of state tuberculosis associations, and to members of the staff of the National Tuberculosis Association. The report appears also in the American Trudeau Society section of the April 1951 issue of THE AMERICAN REVIEW OF TUBERCULOSIS (pp. 496–500).

The subjects considered at the November 1950 meeting by the Clinical Subcommittee are listed below, and the action taken appears in the detailed report published in THE AMERICAN REVIEW OF TUBERCULOSIS.

1. A proposal that the Society sponsor regional interstate conferences similar to those held at Pembine, Wisconsin.
2. Institution of a project for the collection of data on the results of different forms of therapy of pulmonary tuberculosis through appointment of a special subcommittee for this purpose in 1951–1952.
3. Preparation of a revised statement on the current status of antimicrobial therapy in tuberculosis.
4. A recommendation for transmission to the 1951–1952 Annual Meeting Program Committee that carefully constructed symposia, centering around presentations by leading investigators on important and timely topics, be planned and that time be allowed for considerable discussion from the floor.
5. A recommendation that the 1951–1952 Clinical Subcommittee, or its successor, give consideration to the disposition of the so-called "good chronic" patient.

The second meeting of the Clinical Subcommittee, held in January 1951, was devoted exclusively to completion of preparation of the statement "Current Status of Antimicrobial Therapy in Tuberculosis." This statement was published in the American Trudeau Society section of the May 1951 issue of THE AMERICAN REVIEW OF TUBERCULOSIS (pp. 617–623).

The third meeting, held on May 13, 1951, consisted almost entirely of a joint session with the Laboratory Subcommittee.

LABORATORY SUBCOMMITTEE

The Laboratory Subcommittee has held two meetings during the year as follows: (1) November 15, 1950, New York, N. Y., (2) May 13, 1951, Cincinnati, Ohio.

Part of each of these meetings was devoted to a joint session with the Clinical Sub-

committee. As mentioned in the report of that Committee, the individual reports and the joint report were circulated to members of each of the Subcommittees and other groups, and appear in the American Trudeau Society section of the April 1951 issue of THE AMERICAN REVIEW OF TUBERCULOSIS (pp. 496–500).

The subjects considered at the November 1950 meeting of the Laboratory Subcommittee are listed below, and the action taken appears in the detailed report published in THE AMERICAN REVIEW OF TUBERCULOSIS.

1. A standard method of reporting *in vitro* tests of streptomycin resistance of tubercle bacilli as a guide to the clinician.
2. The status of new antibiotics from the experimental point of view.
3. The possibility of performing streptomycin sensitivity tests on tubercle bacilli isolated from all newly admitted patients.
4. Encouragement of more long-term research in the field of biochemical characteristics of bacterial resistance to antibiotics.

At the May 13, 1951 meeting the Laboratory Subcommittee considered further the proposed publication of a standard method of reporting *in vitro* tests of resistance of tubercle bacilli to streptomycin, dihydrostreptomycin, and para-aminosalicylic acid. At the November 1950 meeting it was recommended that the report of a previous Laboratory Subcommittee meeting in 1948 on streptomycin-sensitivity tests be revised and published. Members of the Laboratory Subcommittee have reviewed that report in the interim, and its revision, which will also include para-aminosalicylic acid resistance of tubercle bacilli, is underway. It is expected that it will be published within the near future in THE AMERICAN REVIEW OF TUBERCULOSIS.[1]

At the May meeting the Laboratory Subcommittee made the following recommendations for submission to the Committee on Medical Research:

1. That sources and methods of obtaining BCG vaccine for clinical evaluation be clarified.
2. That the 1951–1952 Laboratory Subcommittee be requested to review the minimal requirements for preparation of BCG vaccine.
3. That the chairman of the 1951–1952 Committee on Medical Research request Dr. Robert J. Anderson, Chief of the Division of Chronic Disease and Tuberculosis of the Public Health Service, to issue a progress report on the laboratory and clinical aspects of BCG vaccination, conducted under the auspices of the Public Health Service.

JOINT MEETING OF CLINICAL AND LABORATORY SUBCOMMITTEES

In joint session the two Subcommittees considered the following subjects at the November 1950 meeting, a report of which was published in the April 1951 issue of THE AMERICAN REVIEW OF TUBERCULOSIS (pp. 496–500).

1. Preparation and publication of a statement with regard to the employment of ACTH and cortisone in the treatment of patients with tuberculosis.
2. Preparation and publication of a statement of the present status of the hemagglutination test.
3. The problem of correlation of *in vitro* and *in vivo* determinations of bacterial resistance to streptomycin.

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[1] Published on pages 105-108 of this issue of THE AMERICAN REVIEW OF TUBERCULOSIS.

In joint session on May 13, 1951, the discussion was concerned solely with the following subjects as the statements mentioned under 1 and 2 above have been published.

1. The problem of correlation of *in vitro* and *in vivo* determinations of streptomycin resistance.
2. The significance of negative bacteriologic reports during or immediately after antimicrobial therapy for tuberculosis.

With regard to the problem of correlation of *in vitro* and *in vivo* determinations of streptomycin resistance, the Subcommittees believed that sufficient information is now available to warrant preparation of a statement which may serve as a guide to those interested in this problem. The statement is now in preparation and, when completed, it is proposed that its contents be made available to the membership of the Society. This can be done through the official journal of the Society, THE AMERICAN REVIEW OF TUBERCULOSIS.

With regard to the second topic discussed, the Subcommittees in joint session unanimously voted to recommend to the Committee on Medical Research that the criteria in *Diagnostic Standards* with respect to bacterial negativity be understood not to apply in the case of patients still on antimicrobial therapy, or recently having completed a course, before the lapse of two or three months following the completion of such a course. The Subcommittees suggested that this recommendation be given suitable publicity, probably in the American Trudeau Society section of THE AMERICAN REVIEW OF TUBERCULOSIS.[2]

At both the November and May meetings, the Subcommittees reaffirmed the decision that it is in the best interests of the Society for them to meet jointly for consideration of many of the laboratory and clinical problems which can best be solved through joint participation of the combined membership.

Respectfully submitted,

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STATEMENT ON CRITERIA FOR "NEGATIVE" SPUTUM IN PATIENTS FOLLOWING ANTIMICROBIAL THERAPY

At its meeting in Cincinnati, May 13, 1951, the Committee on Medical Research agreed with the opinion of its Clinical and Laboratory Subcommittees that the criteria for "negative" sputum presented in the 1950 edition of *Diagnostic Standards and Classification of Tuberculosis* of the National Tuberculosis Association are not properly applicable to patients under, or recently under, antimicrobial chemotherapy, since such therapy may cause a disappearance of bacilli from sputum which is only transient. It was

[2] Published on pages 101 and 102 of this issue of THE AMERICAN REVIEW OF TUBERCULOSIS.

recommended that, pending publication of a new edition of *Diagnostic Standards*, discharge of patients from hospitals and sanatoriums on the basis of "negative" sputum be based on the criteria listed in *Diagnostic Standards* only after the lapse of two to three months following discontinuation of antimicrobial chemotherapy.

THE CLINICAL SIGNIFICANCE OF IN VITRO DETERMINATIONS OF STREPTOMYCIN SENSITIVITY AND RESISTANCE

The problem of the clinical significance of the results of *in vitro* determinations of sensitivity or resistance to varying concentrations of streptomycin[3] is of sufficient practical importance to indicate the desirability of stating the areas of agreement in the light of information presently available. Whereas there is disagreement on details, which may be expected to continue, there is sufficient agreement among representative investigators to warrant making a number of statements bearing on this problem for the guidance of physicians concerned with the antimicrobial therapy of tuberculosis in persons who have had previous streptomycin therapy and in whom it is desirable to determine as accurately as possible the potential usefulness of further streptomycin therapy, and also in the case of those patients whose organisms show resistance during a first course of treatment.

As a recent statement published in this journal[3] has emphasized, the emergence of drug-resistant strains of tubercle bacilli remains the most serious deterrent to the free use of antimicrobial agents in the treatment of tuberculosis. It is essential to employ drugs with tuberculostatic properties with restraint and with skill, only in the presence of definite indications for their use, and according to a regimen best designed to delay the emergence of drug-resistant organisms. At the present time a regimen consisting of 1 gm. of streptomycin every second or third day, with 12 gm. of para-aminosalicylic acid (PAS) daily[3] is recommended as the regimen best suited for the treatment of noncritical forms of tuberculosis. Although the limitations of streptomycin resistance have been reduced with the use of this regimen, they have not been eliminated, and it still is essential to plan the over-all treatment of a case of tuberculosis with the greatest care, especially as to the timing of antimicrobial therapy and surgery. These general principles apply even more strongly where streptomycin and PAS have been previously employed, since some degree of streptomycin resistance may already have occurred. The following statements concerning the clinical significance of the results of *in vitro* determinations of streptomycin sensitivity are to be interpreted as guides to the resumption or continuation of antimicrobial therapy. The emphasis is upon sensitivity to streptomycin (although PAS will nearly always be administered when streptomycin is employed), for emergence of strains of organisms resistant to PAS constitutes a lesser problem when combined therapy is administered.[4]

1. As laboratory tests are usually performed *in vitro* for the determination of streptomycin sensitivity,[5] there is no one concentration, such as 10 γ per ml., which is a dividing line between sensitivity and resistance. There is, rather, a "sliding scale" or range of variation.
2. In spite of some variation in the results of multiple *in vitro* determinations

[3] In this statement, reference to streptomycin will be understood also to refer to dihydrostreptomycin, to which the same principles apply.

[4] Current status of antimicrobial therapy, Am. Rev. Tuberc., (May) 1951, *63*, 617-623.

[5] Methods for the determination of the sensitivity of tubercle bacilli to streptomycin, dihydrostreptomycin, and para-aminosalicylic acid, Am. Rev. Tuberc., 1952, *65*, 105-108.

of streptomycin sensitivity from the same specimen, it is probable that duplicate tests, in the same or in different laboratories, will agree closely for the very sensitive and the very resistant organisms. Greater differences may be expected with organisms in the intermediate range of streptomycin sensitivity, but these differences probably are of little clinical significance.

3. There is good correlation between the results of *in vitro* determinations of streptomycin sensitivity and *in vivo* therapeutic response at the extremes of streptomycin concentrations *in vitro*. At low levels of streptomycin resistance *in vitro* there is good clinical evidence of effectiveness of streptomycin therapy; at high levels of streptomycin resistance *in vitro* (500 to 1,000 γ per ml. or over) there is evidence of relative ineffectiveness of streptomycin therapy. At intermediate ranges of streptomycin resistance *in vitro* the clinical response to streptomycin therapy is variable and is dependent on many factors, such as the resistance of the host, the nature of the therapeutic problem, the dynamic status of the disease, et cetera, as well as upon the chemotherapeutic effect.

4. Regardless of the results of *in vitro* determinations of streptomycin sensitivity, even at the lower concentrations, there is evidence that the effectiveness of streptomycin therapy is frequently reduced if there has been prior streptomycin treatment.

5. After previous streptomycin therapy, if a clinical indication for resumption of antimicrobial therapy exists in the presence of *in vitro* reports of streptomycin resistance, there is evidence that streptomycin will exert some bacteriostatic effect when reports indicate resistance to 10 γ per ml. and even when they indicate partial resistance to 100 γ per ml. Under these circumstances many patients respond to combined therapy with streptomycin and PAS as if their organisms were completely sensitive, and others respond less favorably. Evidence of the continued effectiveness of streptomycin combined with PAS in the presence of reports of *in vitro* resistance to concentrations of streptomycin higher than 100 γ per ml. is lacking.

6. In the individual patient still receiving antimicrobial therapy, every effort should be made to assess the response to that therapy on clinical grounds, even though *in vitro* reports of streptomycin resistance are lacking or indicate streptomycin resistance. The decision for the continuance of such therapy should be made on such clinical criteria.

7. For laboratories equipped to carry out *in vitro* tests of streptomycin resistance, it is suggested that it is valuable to test the resistance of *M. tuberculosis* in several different concentrations of streptomycin, including, in addition to the control tube not containing streptomycin, tubes containing the following concentrations of streptomycin, or their close counterparts: 10 γ per ml., 100 γ per ml., and 1,000 γ per ml.

8. It is believed advisable to make such determinations of streptomycin resistance for the following reasons:

a. The results assist in determining the prognosis of the patient, with respect to the likelihood of obtaining a response to a particular course of antimicrobial therapy.

b. The results permit more accurate timing of indicated surgical procedures in connection with a course of antimicrobial therapy for, after streptomycin resistance has begun to appear, further therapy may have diminishing returns

and relapse prior to definitive surgical treatment is more likely to occur, thus limiting the period in which surgery may be performed with optimal results.

c. The results serve as indications as to when other antimicrobial agents (other than streptomycin and PAS) now available and those yet to be developed may more effectively be introduced into the course of therapy.

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METHODS FOR THE DETERMINATION OF THE SENSITIVITY OF TUBERCLE BACILLI TO STREPTOMYCIN, DIHYDROSTREPTOMYCIN, AND PARA-AMINOSALICYLIC ACID

While both solid and liquid media have been used for the determination of sensitivity of tubercle bacilli to streptomycin, dihydrostreptomycin, and para-aminosalicylic acid a solid medium is preferable. It permits the determination of sensitivity by direct inoculation from sputum concentrates, thus furnishing a better indication of the relative numbers of drug-resistant and -sensitive tubercle bacilli, and saving considerable time in reporting the results of such tests.

Determination of Streptomycin and Dihydrostreptomycin Sensitivity of Tubercle Bacilli

Preparation of Egg Yolk-Potato Flour Medium (American Trudeau Society (ATS) medium)

Egg yolk	500 ml.
Potato flour water (containing 2 per cent glycerol)	500 ml.

1. The potato flour water is made by adding 20 gm. of potato flour to 500 ml. of 2 volumes per cent glycerol water in a flask or beaker. The mixture is heated to boiling with constant stirring and cooled to 50°C.

2. Egg yolk is obtained by carefully cleaning fresh hens' eggs with wet gauze, rinsing them in alcohol, and separating the egg white and yolks. A proportion of one whole egg to eleven egg yolks is used, and 500 ml. of this combination are obtained.

3. Five hundred ml. of egg yolk are poured into the 500 ml. of potato flour water and to this are added 20 ml. of 1 per cent malachite green solution in 50 per cent alcohol. All ingredients are thoroughly mixed and tubed.

4. The medium is coagulated in a slanted position and sterilized by a single forty-minute stay in an inspissator heated to 90°C. The tubes are incubated for forty-eight hours; contaminations are rare if sterile technique is maintained throughout the procedure.

Egg yolk medium prepared as indicated above will be acid in reaction, with a pH of about 6.5. If the tubes contain too much water of condensation, the excess should be removed.

In addition to the above, the following formula may be used:

Buffered Egg-Potato Medium (Löwenstein-Jensen)

Salt Solution:		
Monopotassium phosphate	2.4	gm.
Magnesium sulfate	0.24	gm.
Magnesium citrate	0.6	gm.
Asparagin	3.6	gm.
Glycerol	12	ml.
Distilled water	600	ml.
Potato flour	30	gm.
Egg fluid	1,000	ml.
Malachite green, 2 per cent aqueous solution	20	ml.

1. *Salt and flour solution:* The salt solution is heated in a pot until all of the salts are dissolved. Then it is poured into a flask and heated in an Arnold sterilizer at 100°C. for two hours. The next day 30 gm. of potato flour are added to the flask and the mixture is boiled, with continual shaking or stirring, until the content is clear. It is allowed to cool to 56°C. before the egg fluid is added.

2. *Egg fluid:* Fresh eggs, cleansed with wet gauze and rinsed in alcohol, are broken into a sterile flask and thoroughly homogenized by shaking or stirring.

3. One liter of egg fluid is thoroughly mixed with the content of the flask of salt solution and to this are added the 20 ml. of malachite green solution. This mixture is filtered through sterile gauze and delivered into 150 mm. Pyrex test tubes. The medium is solidified in a slanted position by keeping it at a temperature of 85° to 88°C. for forty minutes. The pH of the medium prepared as above is approximately 6.8. An Arnold steam sterilizer, carefully watched to keep the temperature within the proper limits, may be used. After this final step, the tubes are stored in a refrigerator. A given batch of the medium should be used within four weeks.

Dilutions of Streptomycin to Be Added to Medium

Streptomycin is added to the medium in the quantities indicated below. It is not necessary to prepare dihydrostreptomycin medium since tubercle bacilli, which are sensitive to the one drug, are simultaneously and equally sensitive to the other. It will be noted that streptomycin is added in twice the required strength. The addition of the double quantity is based upon studies by Drummond and co-workers[8] which indicate that approximately 50 per cent of streptomycin is destroyed during the process of inspissation at 85°C. for one hour. Since there is no certainty that exactly 50 per cent is destroyed, it must be recognized that the quantities recorded as present in the finished medium represent an approximation. This fact, however, does not rob the test of its value when performed by experienced personnel provided with laboratory facilities adequate to control rigorously the time and temperature of inspissation and the uniformity of composition of each batch of medium.

Before inspissation, the medium should be divided into four parts:

To part *one*, add nothing
To part *two*, add sufficient streptomycin to make concentration of 6 γ per ml.
To part *three*, add sufficient streptomycin to make concentration of 20 γ per ml.
To part *four*, add sufficient streptomycin to make concentration of 200 γ per ml.

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[8] Drummond, M. C., Lewis, G. T., and Cummings, M. M.: The effect of heat on streptomycin and para-aminosalicylic acid in tuberculosis culture medium, Dis. of Chest, 1951, *19*, 158.

For research purposes a tube containing 2,000 γ per ml. may be added to the series.

Chemical assay of the available streptomycin in the finished medium reveals that the final concentrations of streptomycin are approximately 3.0, 10.0, 100, and 1,000 γ per ml. instead of the original concentrations of 6, 20, 200, and 2,000.

Dilutions of Para-Aminosalicylic Acid to Be Added to Medium

Sensitivity tests to para-aminosalicylic acid are made on solid medium, using either ATS or Löwenstein-Jensen medium.

To either of the above named media, a Seitz-filtered water solution of the sodium salt of para-aminosalicylic acid is added aseptically in sufficient amount to give a final concentration of 0.1, 1.0, 10, and 25 mg. of pure para-aminosalicylic acid per 100 ml. of medium.

The para-aminosalicylic acid sensitivity tests should be performed on sputum or other specimens in the same manner as for streptomycin sensitivity, as should be the recording and reporting of such tests.

Sensitivity Tests Performed Directly from Sputum or Other Specimens

Equal amounts of the concentrates should be inoculated on tubes of medium containing each concentration of streptomycin or para-aminosalicylic acid, and on a tube of the same medium containing no drug.

After inoculation, the medium should be incubated at 37°C. and examined for growth of tubercle bacilli every seven days for a total of six weeks. Reports may be made at two, three, or four weeks, depending upon when growth is adequate. Negative cultures may be held longer than six weeks as diagnostic cultures only.

The recording and reporting of sensitivity-test results should be made by comparing the amount of growth on the drug-containing medium with the amount of growth in the control tubes. When growth is obtained only on the control tube, the culture is considered completely sensitive (nonresistant). When similar growth is obtained on the drug-containing and the control tubes, the culture is considered completely resistant (non-sensitive). When there is definitely less growth on the drug-containing tubes as compared with the controls, the culture is considered partially resistant (partially sensitive) to the concentration of drug present.

The tests are considered unsatisfactory and should be repeated when the following conditions occur:

a. When contamination makes the comparison unreliable.
b. When irregularity of growth is such that the sensitivity of the culture cannot be determined; for example, when an intermediate tube shows no growth.
c. When there are fewer than 10 colonies on the control.

Repeat tests should then be performed with the pure cultures, using a composite of all of the available colonies on the control tube.

Indirect or Subculture Method of Performing Streptomycin and Para-Aminosalicylic Acid Sensitivity Tests

If only a few colonies chance to grow on the control tube and none on the drug-containing tubes, the indirect method must be used. In such a case, it is necessary to triturate a representative sample of the colonies in either a small amount of Tween-albumin medium or Tween-containing saline, and to plant 0.1 cc. of this culture or suspension on

the same series of control and drug-containing solid medium. This should always be marked "Subculture Sensitivity Test."

Suggested Form for Recording Results of Streptomycin, Dihydrostreptomycin, and Para-Aminosalicylic Acid Sensitivity Tests

RESULTS OF SENSITIVITY TESTS $\frac{\text{DIRECT}}{\text{SUBCULTURE}}$ (Check one)

Hospital.....
Patient.....
Date of Culture..... Laboratory Number of Culture.....

SM or DHSM in micrograms per ml. of medium	14 days	21 days	28 days	35 days	42 days
0					
3					
10					
100					
1,000					

The same form is used for recording para-aminosalicylic acid sensitivity tests, except that in the first column PAS in milligrams per 100 ml. of medium is substituted, and the following concentrations may be used: 0.0, 0.1; 1.0, 10, and 25 mg. per 100 ml. of medium.

The members of the Laboratory and Clinical Subcommittees recognize that the foregoing recommended procedures for performing streptomycin and PAS sensitivity tests may not be acceptable to all. However, after careful consideration of the problems involved and the correlation of the tests performed by these methods with clinical material available from the Veterans Administration studies by Tucker,[6, 7] it would appear that the results of the tests furnish adequate information for immediate clinical use. As indicated on page 106, the dilutions represent rather gross approximations of the recorded strengths. It is hoped that superior methods will be developed in the future. Needless to say, the procedure for determination of sensitivity will be revised from time to time as better methods are devised.

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[6] Quarterly Progress Report by the Veterans Administration Hospitals cooperating in a study of the chemotherapy of tuberculosis, July 1, 1951.

[7] Transactions of the National Tuberculosis Association meeting, Cincinnati, May 1951.

NOTES

MEMBERSHIP IN THE AMERICAN TRUDEAU SOCIETY

Physicians in good standing in the medical profession in the United States, Canada, and other countries may apply for membership in the Society. In addition to the nationally constituted American Trudeau Society, there are state and regional ATS sections in the United States with which a physician may become affiliated. The state and regional meetings of the ATS sections provide opportunities for additional association with physicians and surgeons interested in pulmonary and other thoracic diseases.

The dues for Active Membership in the American Trudeau Society are $12.00 per year. Active Membership includes membership in the National Tuberculosis Association, a year's subscription to THE AMERICAN REVIEW OF TUBERCULOSIS, a subscription to the monthly BULLETIN of the Association, and the TRANSACTIONS of the Annual Meeting of the National Tuberculosis Association.

Associate membership, at the special rate of $5.00 per year, is available, provided the application for such membership is made within five years of graduation from medical school. This includes membership in the National Tuberculosis Association, but not a subscription to THE AMERICAN REVIEW OF TUBERCULOSIS.

MEDICAL RESEARCH FELLOWSHIPS

The Medical Fellowship Board of the National Research Council is now accepting applications for postdoctoral research fellowships for 1952–1953 under the following programs:

Fellowships in the Medical Sciences. There are two groups of these fellowships, one supported by The Rockefeller Foundation, and another by The Lilly Research Laboratories. They provide opportunity for training in research in all branches of medical science. The Rockefeller Fellowships are open to citizens of the United States or Canada; the Lilly Fellowships, only to citizens of the United States. Fellows must hold the M.D. or Ph.D. degree. The awards are intended for recent graduates who, as a rule, are not more than thirty years of age.

Fellowships in Tuberculosis are made available under a grant from the National Tuberculosis Association. These awards are limited in number and are designed to promote the training and development of investigators in fields related to tuberculosis. They are open to citizens of the United States who are graduates of American schools and who, as a rule, are not more than thirty years of age. Preference will be given to applicants who have the M.D. or Ph.D. degree; only in exceptional circumstances will a fellowship be awarded to an applicant without either of these degrees.

Fellows will be appointed at a meeting of the Medical Fellowship Board early in March, 1952. Applications for consideration at this meeting must be filed on or before December 15, 1951. Appointment may begin at any time determined by the Board. For further information about these fellowships, address the Secretary of the Medical Fellowship Board, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

1952 ANNUAL MEETING OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians will hold its eighteenth Annual Meeting in Chicago, June 5–8, 1952. Physicians wishing to submit papers for this meeting should send their titles and abstracts to Dr. Harold G. Trimble, 2930 Summit Street, Oakland 9, California. The Annual Meeting of the College will precede the annual meeting of the American Medical Association to be held in Chicago, June 9–13, 1952.

INTERNATIONAL UNION AGAINST TUBERCULOSIS

COMMITTEE OF EXECUTIVE DIRECTORS OF NATIONAL ORGANIZATIONS

At Copenhagen in 1950 it was decided that, since executive directors of national bodies affiliated with the International Union play such an important role in the tuberculosis work of their countries, it would be a useful innovation for them to meet and exchange views on matters of interest. The first of these meetings was held in the King George V Hotel, Paris, on Monday and Tuesday, September 10 and 11, 1951, when the Committee of Executive Directors was formally constituted under the chairmanship of Dr. Harley Williams. Nineteen countries sent delegates, and twenty-three members were present.

Dr. T. Gedde-Dahl (Norway) opened the proceedings with a comprehensive paper describing, not only the organization of the Norwegian Association, but drawing parallels between different methods of organization and administration in various countries.

At the second session the meeting discussed the subject of "Methods of Raising Funds for Antituberculosis Work", introduced by Professor Pilod (French National Committee) and seconded by M. Lucien Viborel. At the close of the discussion Dr. James E. Perkins (U. S. A.) raised the important question of the proposed Christmas "seal" which is to be issued by the World Health Organization (the proceeds being divided 25 per cent for WHO, and 75 per cent for the country in which seals are sold). After much discussion, a resolution was proposed and adopted by thirteen votes to none, with two abstentions, to the effect that the Council of the International Union Against Tuberculosis, an international agency in official relationship with WHO, requested the Executive Board of WHO to reconsider the proposed annual sale of a WHO seal. This request was made on the grounds that WHO is an official body supported by tax funds, whereas the voluntary tuberculosis associations depend—and for long have depended—for their chief support on their Christmas Seal Sales, and that the proposed WHO Seal Sale might well lead to confusion and a reduction in support of the voluntary organizations.

At the third session Dr. James E. Perkins (U. S. A.) read a paper upon the relationships which the National Tuberculosis Association has developed in the U. S. A. between physicians and nonmedical persons who have become interested in the campaign against tuberculosis and who take part in various activities of the Association and its affiliated associations. He referred especially to the training and employment of professional but nonmedical workers. From the subsequent discussions it was clear that, while in the western part of the European continent laymen and nonprofessional workers do not play any large part in antituberculosis work, circumstances are quite different in Great Britain and the Scandinavian countries, parts of Eastern Europe and the Far East, where the cooperation of nonmedical personnel is warmly advocated.

At the last session Dr. J. Kroondijk (Holland) described the organization of tuberculosis work in his country, with particular reference to propaganda and health education, using the cinema film. A new cinema production entitled *Men and Microbes*, directed by Max de Haas, was exhibited. The subsequent discussion upon health education through the cinema was one of the most interesting of the whole meeting. It was clear that at least two kinds of film are needed for health education: short instructional films which must be made in the country where they are to be exhibited; and more expensive and elaborate propaganda productions with wider value and implications, more suitable for general use.

Plans are in hand for holding another Conference of Secretaries in 1952—possibly in Rio de Janeiro—and further conferences in subsequent years, the steering committee responsible to work in close liaison with the Secretary General of the International Union. The members of this steering committee are Dr. Harley Williams, Dr. Pedro M. Sturbe, and Dr. James E. Perkins.

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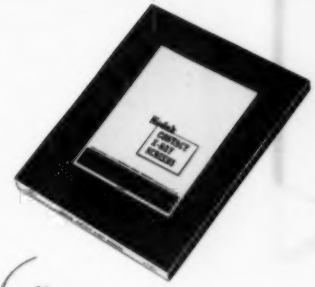

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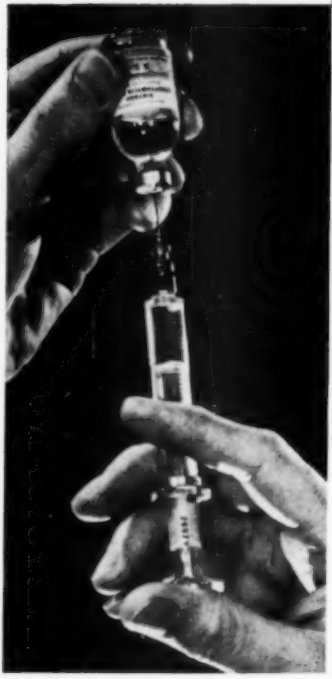

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NATIONAL TUBERCULOSIS ASSOCIATION

ANNUAL MEETING ***MAY 26–29, 1952***

BOSTON, MASSACHUSETTS

The annual meeting of the National Tuberculosis Association will be held in Boston, Massachusetts, May 26–29, 1952. The Statler Hotel will be headquarters.

Some 1500 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Arrange to share a twin bed room if possible.

Application for room reservations should be made directly with the hotel of your choice.

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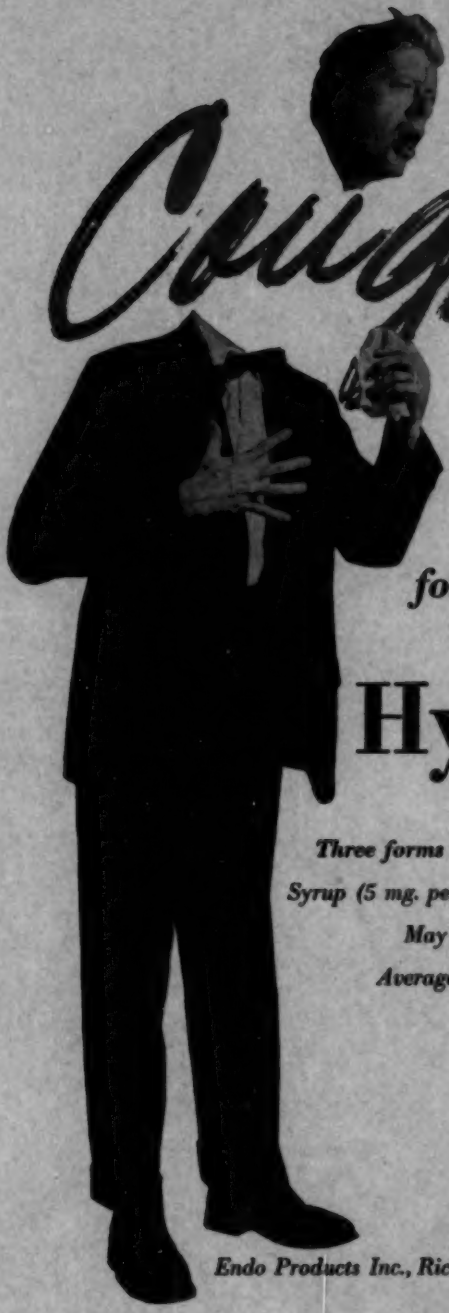

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